FACULTY OF ENGINEERING AND ARCHITECTURE

DEPARTMENT OF ELECTROMECHANICAL, SYSTEMS AND METAL ENGINEERING
RESEARCH GROUP ELECTRICAL ENERGY LAB

MAGNETISM FOR BIOLOGY AND MEDICINE

European School on Magnetism

dr. Annelies Coene

11-09-2021

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WHO AM I?

Annelies Coene
Civil engineer: biomedical engineering, UGent, Belgium (2011)
Teaching Assistent UGent, Belgium (2011-2017)
PhD in biomedical engineering (2017)
Junior postdoctoral fellow Flemish Scientific Research Fund (2017-2021)
Senior postdoctoral fellow Flemish Scientific Research Fund (2021-2025)

Guest scientist PTB, Berlin (2013, 2015)
Guest scientist UMIT, Austria (2017)

Research interests: biomedical applications of magnetic nanoparticles, inverse problems, optimization, hybrid AI, theranostic applications

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EEMMECS

Faculty of Engineering & Architecture

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Department of Electromechanical, Systems and Metal Engineering

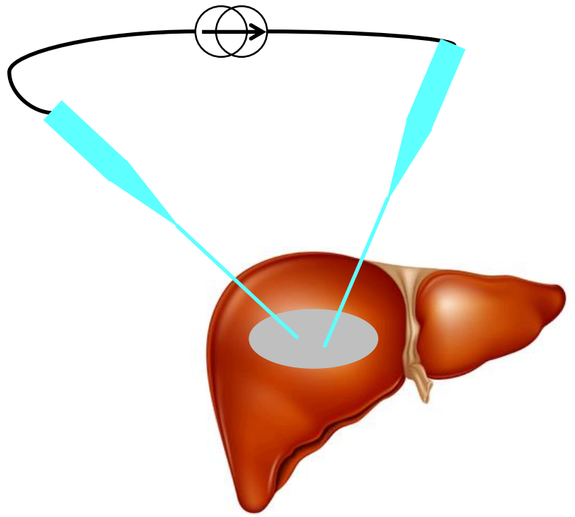
- *Since 2004:* Research on inverse problems and optimal design in electromagnetism with focus on:
  - Optimal design of shielding and electromagnetic devices
  - Magnetic material reconstruction
  - Non-destructive evaluation
  - Bio-electromagnetic optimization and inverse problems

- *Since 2013*: Hybrid AI

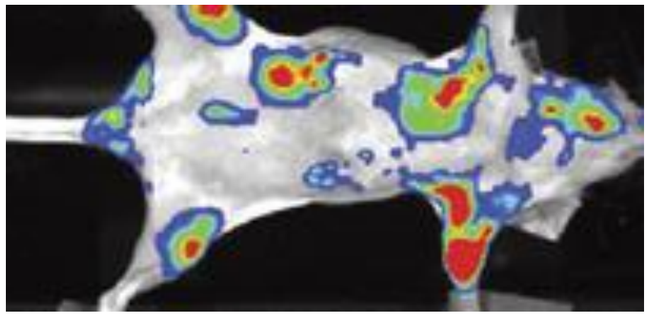
BIO-ELECTROMAGNETIC APPLICATIONS

Electroencephalography

Transcranial Magnetic Stimulation



Radiofrequency ablation



Non-invasive imaging of magnetic nanoparticles

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CONTENTS

- Magnetic Resonance Imaging
- Neuromagnetism
- Magnetic stimulation
- Medical applications of magnetic nanoparticles

MAGNETIC RESONANCE IMAGING

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MAGNETIC RESONANCE IMAGING: INTRODUCTION

- Anatomic images with fine resolution
- Unparalleled soft tissue contrast
- No radiation
- First images in 1973

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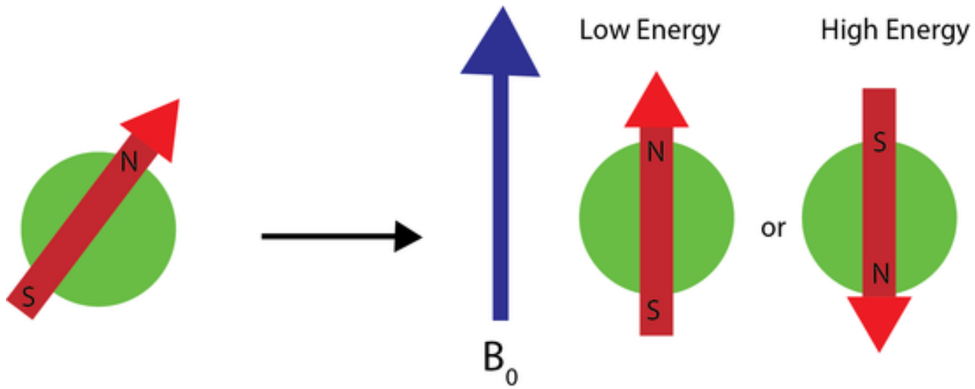
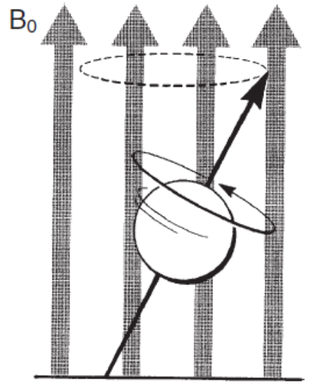
MAGNETIC RESONANCE IMAGING: PHYSICAL PRINCIPLES

- Homogeneous magnetic field B_0 ~T

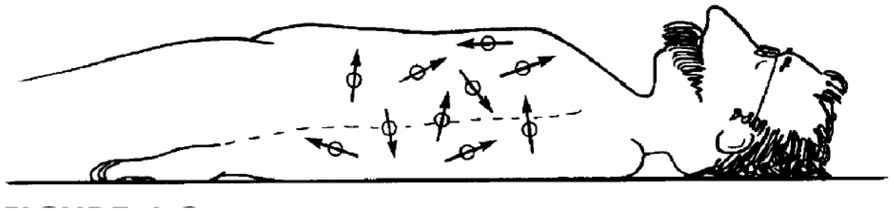


Nucleus with uneven amount of protons or neutrons expresses a magnetic moment



Additionally, a precession occurs around the magnetic field. Stewart, al. (2014)

- Hydrogen is abundant in the body (~80%) -> large signal when placed in magnetic field



Without a magnetic field, no net magnetization is measurable Stewart, et al. (2014)

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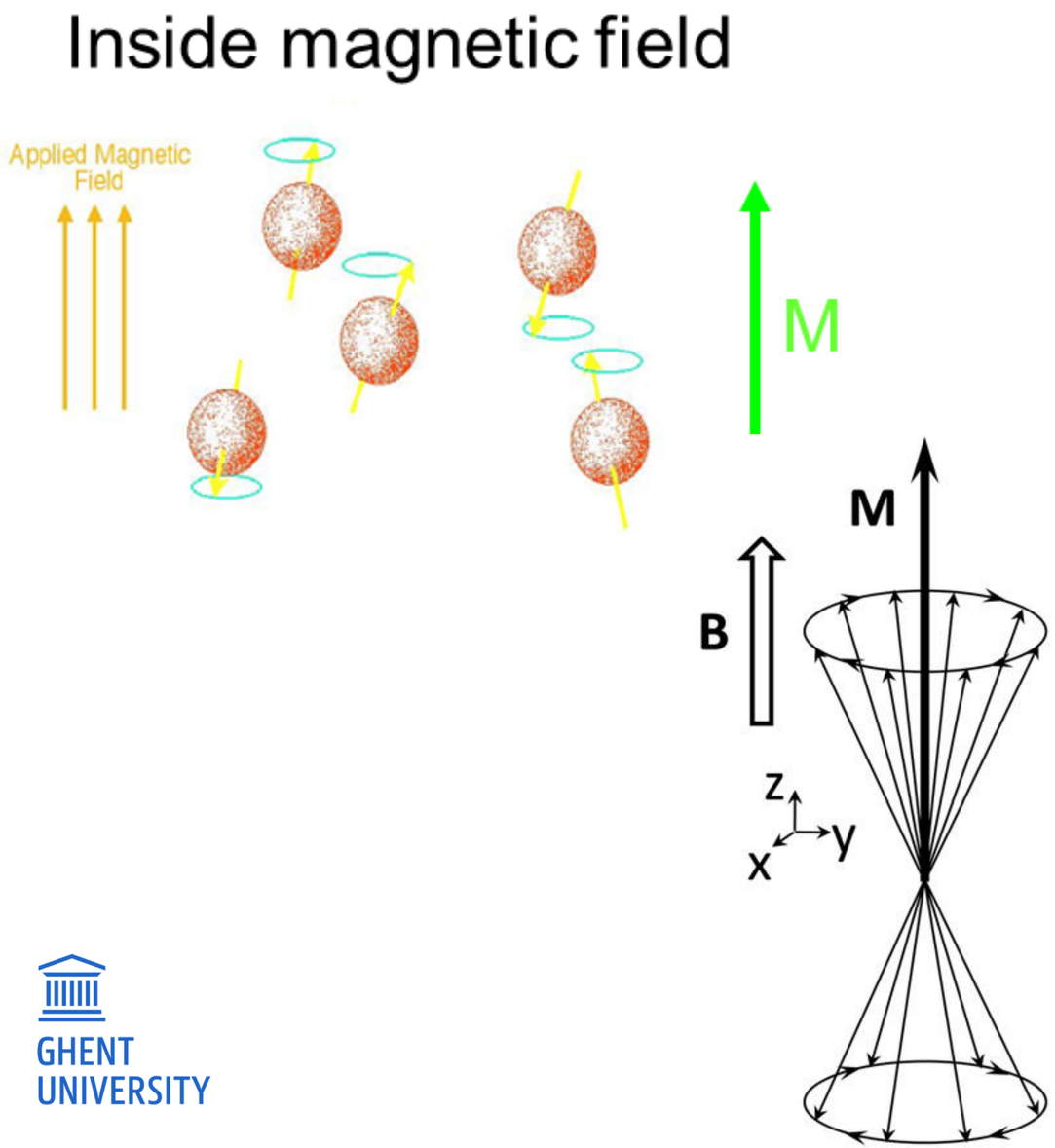
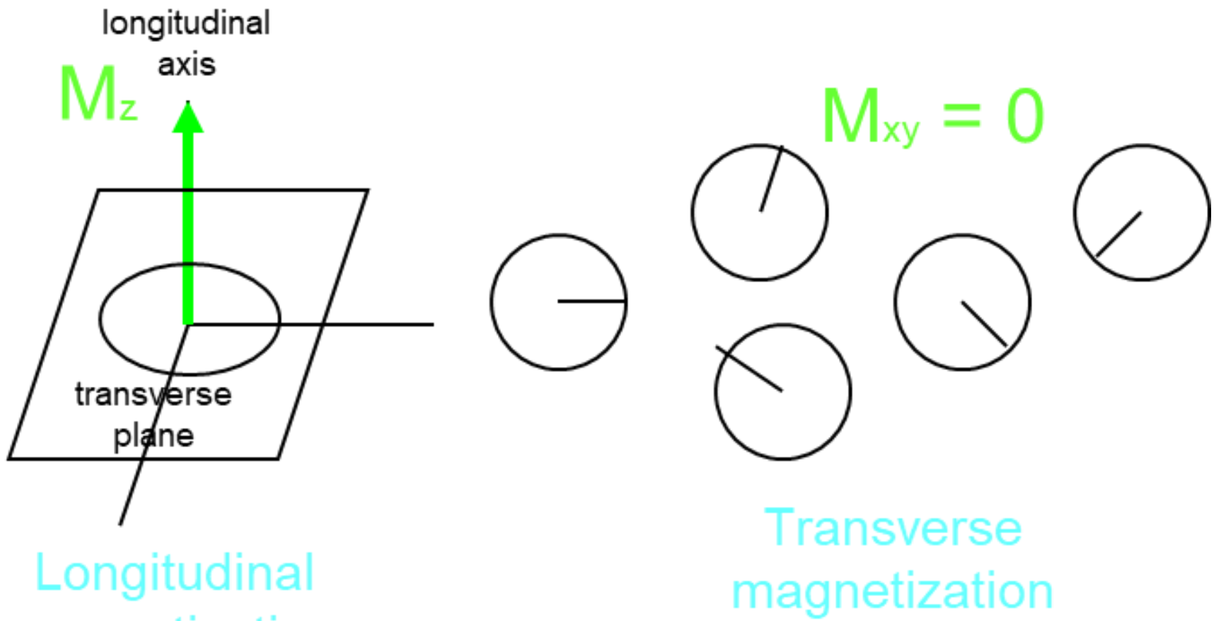
MAGNETIC RESONANCE IMAGING: PHYSICAL PRINCIPLES





Longitudinal magnetization

Transverse magnetization

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MAGNETIC RESONANCE IMAGING: LARMOR FREQUENCY

What is the frequency of the precession?

$$f_o = \gamma B_o$$

where f_o is the frequency of precession (or resonant freqeuncy) and γ is the gyromagnetic ratio.

If B_0 is 1 T, then the precessional frequency is 42 MHz for a proton. Likewise, at 1.5 T the precessional frequency is 63 MHz.

Fundamental equation of MRI, the Larmor equation

Nucleus	Gyromagnetic Ratio (MHz/T)
^{1}H	42.6
^{19}F	40.1
^{31}P	17.2
^{23}Na	11.3
^{13}C	10.7
^{2}H	6.5
^{17}O	5.8
^{39}K	2.0

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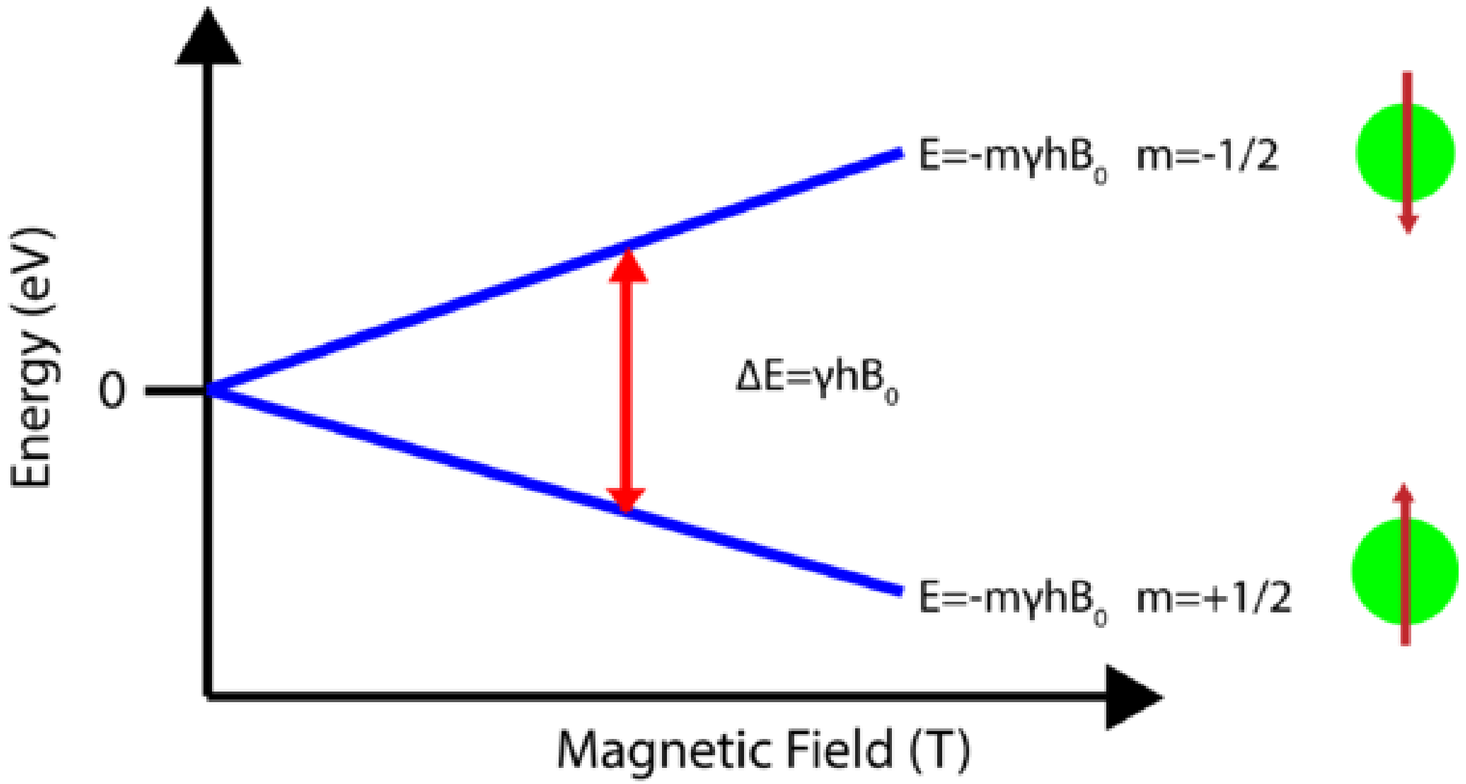
MAGNETIC RESONANCE IMAGING: ENERGY LEVELS



m = magnetic quantum number (1/2 for H)
γ = gyromagnetic ratio
h= Planck's constant

there are 2m+1 energy levels

How many protons are on each level?

The Boltzmann equation describes the population ratio of the two energy states: $N^-/N^+ = e^{-\Delta E/kT}$ k the Boltzmann constant, T temperature

- Larger B_0 produces larger net magnetization M, lined up with B_0

- Thermal motions try to randomize alignment of proton magnets

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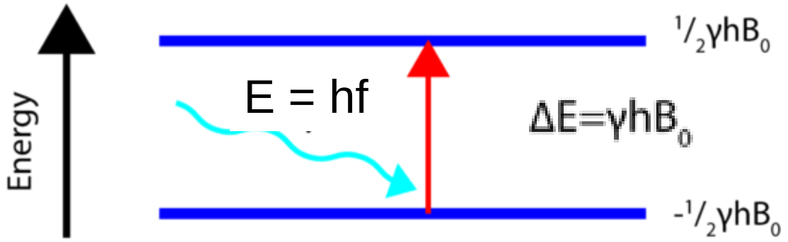
MAGNETIC RESONANCE IMAGING: RESONANCE

– Magnetic resonance: when these nuclei are additionally exposed to a magnetic field pulse of the right frequency, they can take up energy from this field and reach the higher energy level



The energy of a photon (electromagnetic radiation) is represented by
$E=hf$
and thus the frequency necessary for absorption to occur is:
$f=\gamma B_0$ -> Larmor equation f_0

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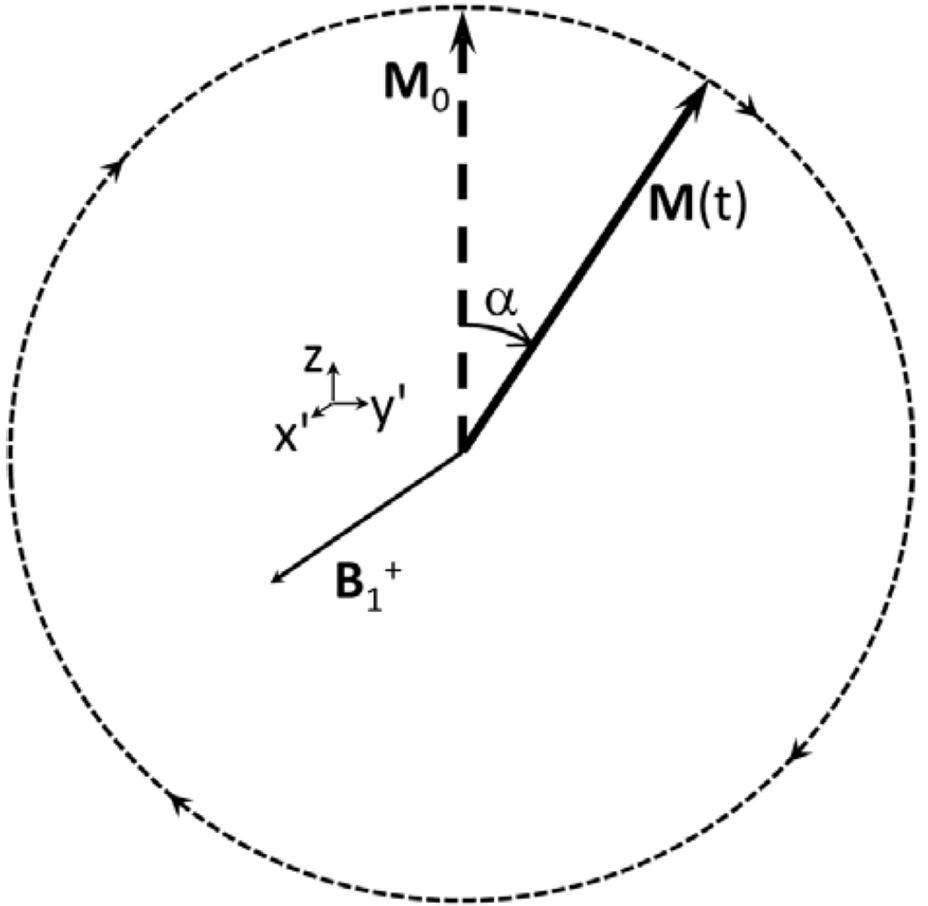
MAGNETIC RESONANCE IMAGING: RADIOFREQUENCY PULSE

magnetic (B_1) field having a frequency equal to f_0 and field components oriented perpendicular to B_0

components of any RF field in the transverse (x–y) can be expressed as circularly polarized components rotating clockwise and counter-clockwise within the transverse plane

One of the two rotating components will rotate in the same direction as nuclear precession, appear as a static field in the frame of reference of the nuclei B_1^+



Rotating reference frame around z

$$\mathbf{dM} = \mathbf{M} \times \mathbf{B}$$

$$a = \gamma |B_1^+| \tau.$$

'tip angle' α induced by a B_1^+ field in a 'rectangular pulse' having constant amplitude applied for a duration τ

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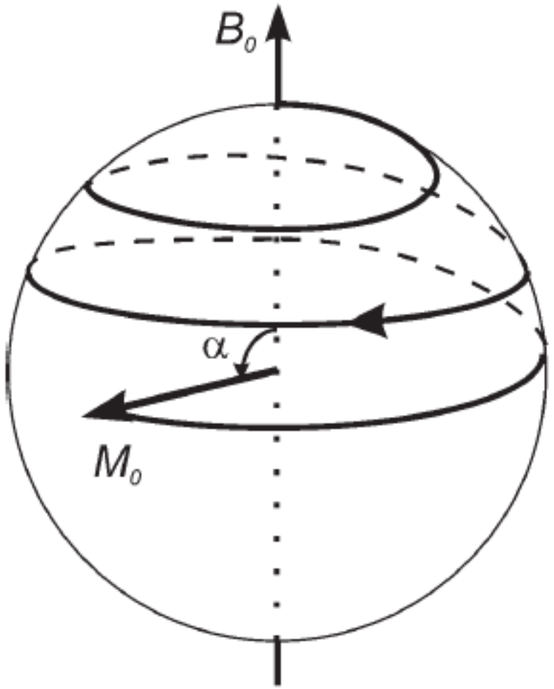
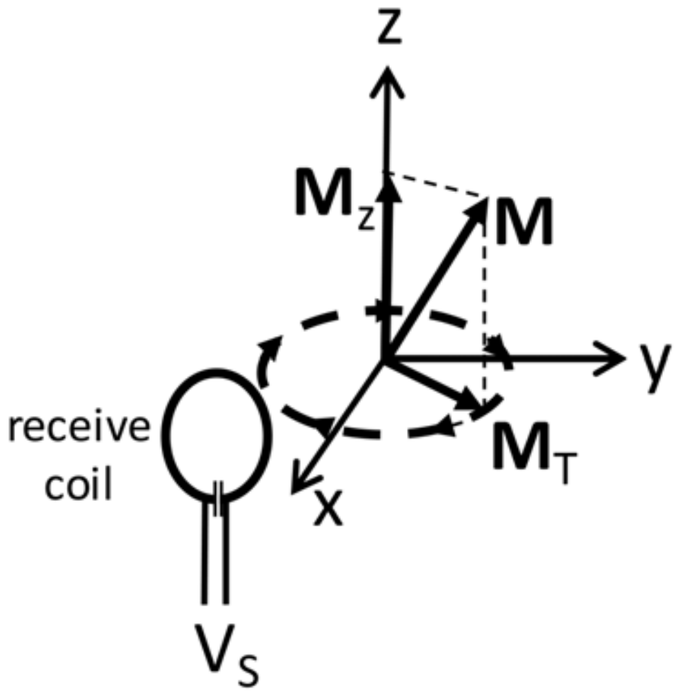
MAGNETIC RESONANCE IMAGING: RADIOFREQUENCY PULSE



Outside the rotating frame, the net magnetization executes a spiral path on the surface of a sphere

Now a moving transverse component of the net magnetization is created, which can be measured with a coil in the transverse plane



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MAGNETIC RESONANCE IMAGING: RELAXATION

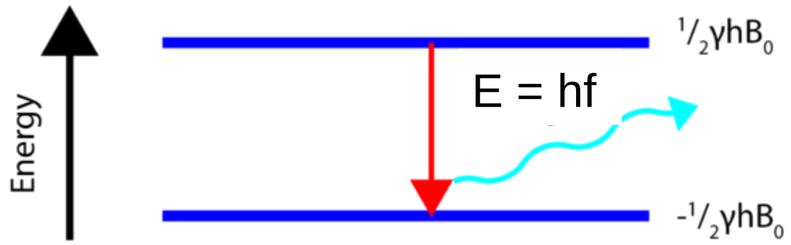
After removal B_1

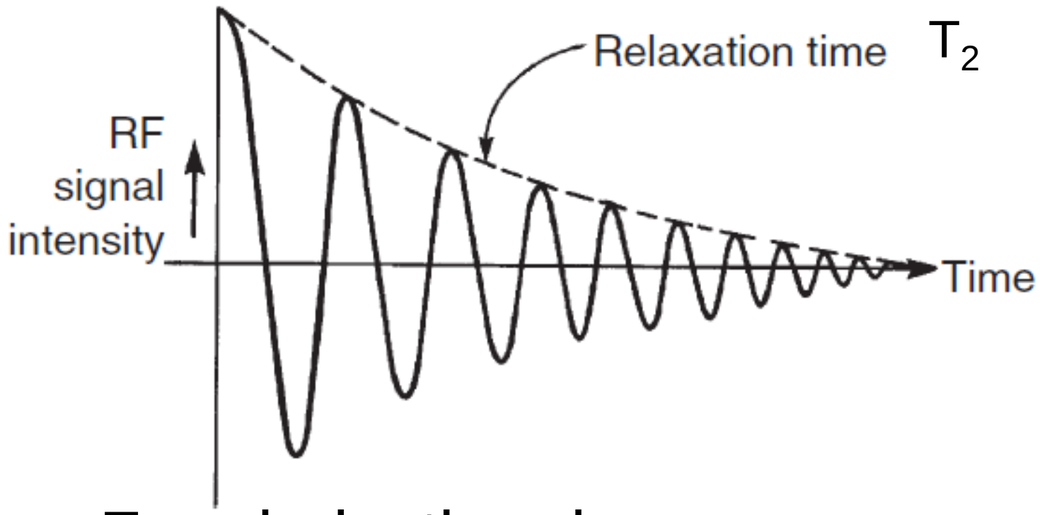
Relaxation through 2 mechanisms:

Longitudinal (spin-lattice) relaxation T_1 : dissipation of energy to the lattice

Transverse (spin-spin) relaxation T_2 : loss of phase coherence between spins

- Materials in human imaging T1 > T2
- $\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{\gamma \Delta B}{\Delta B}$. Magnetic field inhomogeneities in B0 make spins dephase faster





Free induction decay

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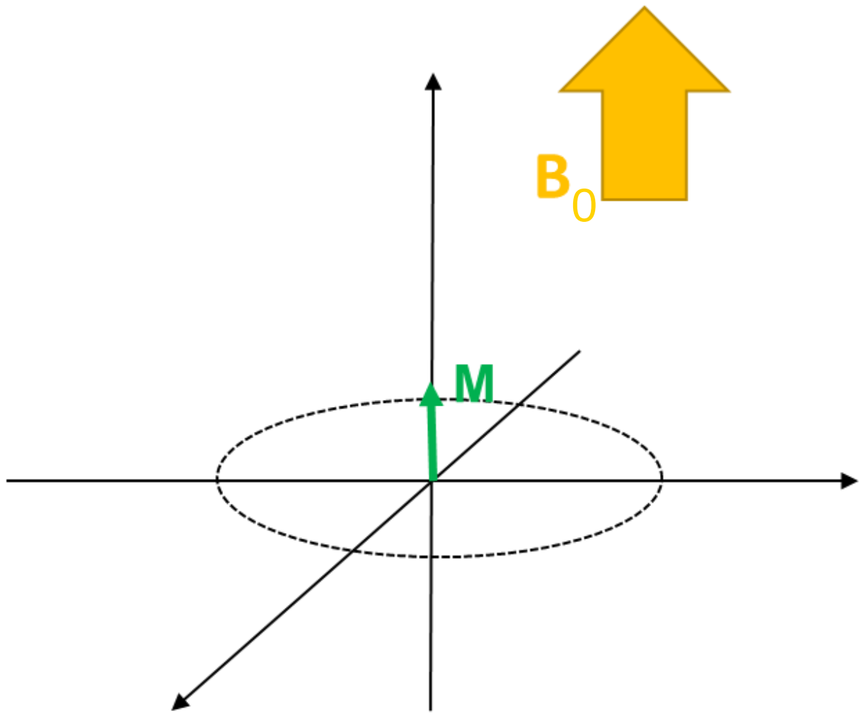
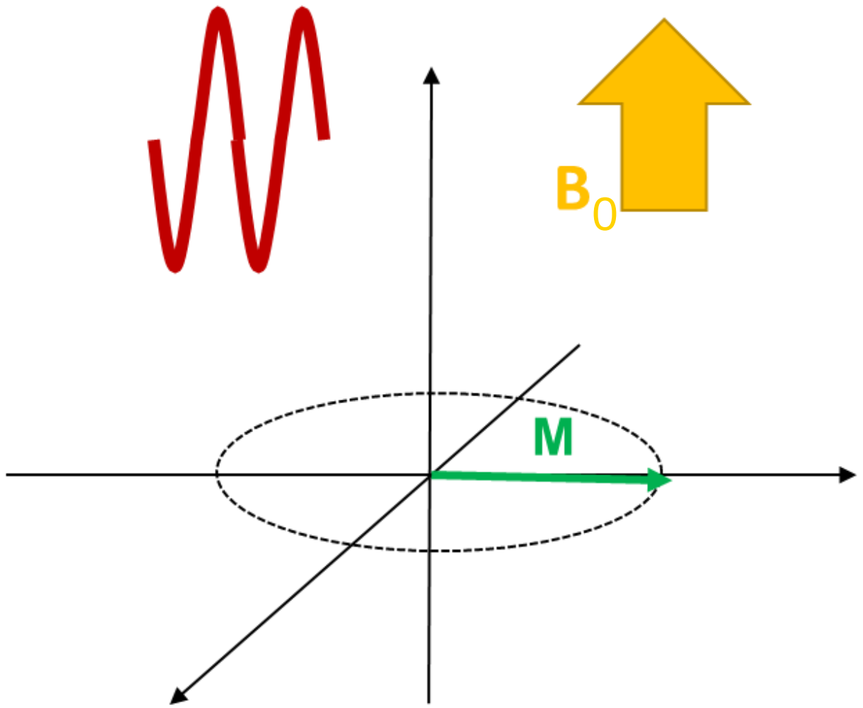
MAGNETIC RESONANCE IMAGING: OVERVIEW

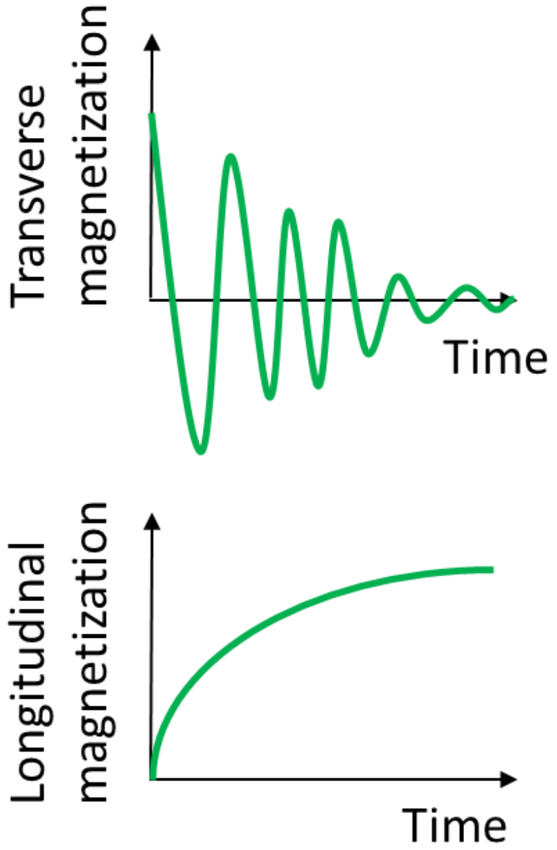
a) Before applying a 90° pulse



b) After applying a 90° pulse



c) T_1 and T_2 relaxation



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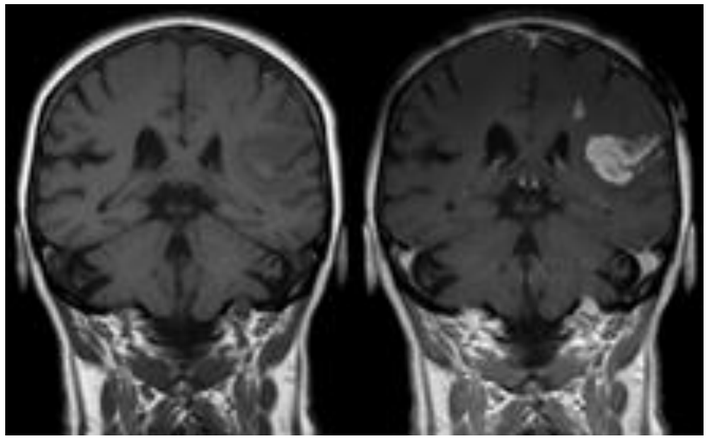
MAGNETIC RESONANCE IMAGING: TISSUE SIGNAL

Tissue	T1 (msec)	T2 (msec)
Water/CSF	4000	2000
Gray matter	900	90
Muscle	900	50
Liver	500	40
Fat	250	70
Tendon	400	5
Proteins	250	0.1- 1.0
Ice	5000	0.001

https://mri-q.com/uploads/3/4/5/7/34572113/5092979_orig.gif

MRI images can be T_1 or T_2 weighted. In the first type, tissues expressing a fast T_1 relaxation, have a bright signal in the obtained image, while tissues with longer T_1 relaxation, result in dark values. In the latter type, tissues with a fast T_2 relaxation have a dark signal.

Although MRI has a fine resolution, in some cases it is a challenge to create enough contrast between pathological tissue and its surrounding healthy tissue. This contrast can be achieved by introducing MRI contrast agents which speed up T_1 and/or T_2 at the unhealthy tissue.



Contrast agents typically employed in MRI, consist of a heavy metal ion, such as gadolinium or manganese, which is encompassed by a chelate that is used to make the agent non-toxic

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MAGNETIC RESONANCE IMAGING: BLOCH EQUATION

the effects of these two relaxation processes on M in the presence of no applied fields but B0 can be described mathematically:

$$M_z(t) = M_0 - (M_0 - M_z(0))\mathrm{e}^{-t/T_1}$$

$$|M_T(t)| = |M_T(0)|\mathrm{e}^{-t/T_2}$$

Combining everything: *Bloch equation*

Manipulation of M with magnetic fields

Transverse relaxation

Return to equilibrium magnetization

$$\frac{\mathrm{d}\mathbf{M}}{\mathrm{d}t} = \gamma(\mathbf{M} \times \mathbf{B}) - \left(\frac{M_x}{T_2}\mathbf{a}_i + \frac{M_y}{T_2}\mathbf{a}_j + \frac{M_z - M_0}{T_1}\mathbf{a}_k\right)$$

a is unit vector

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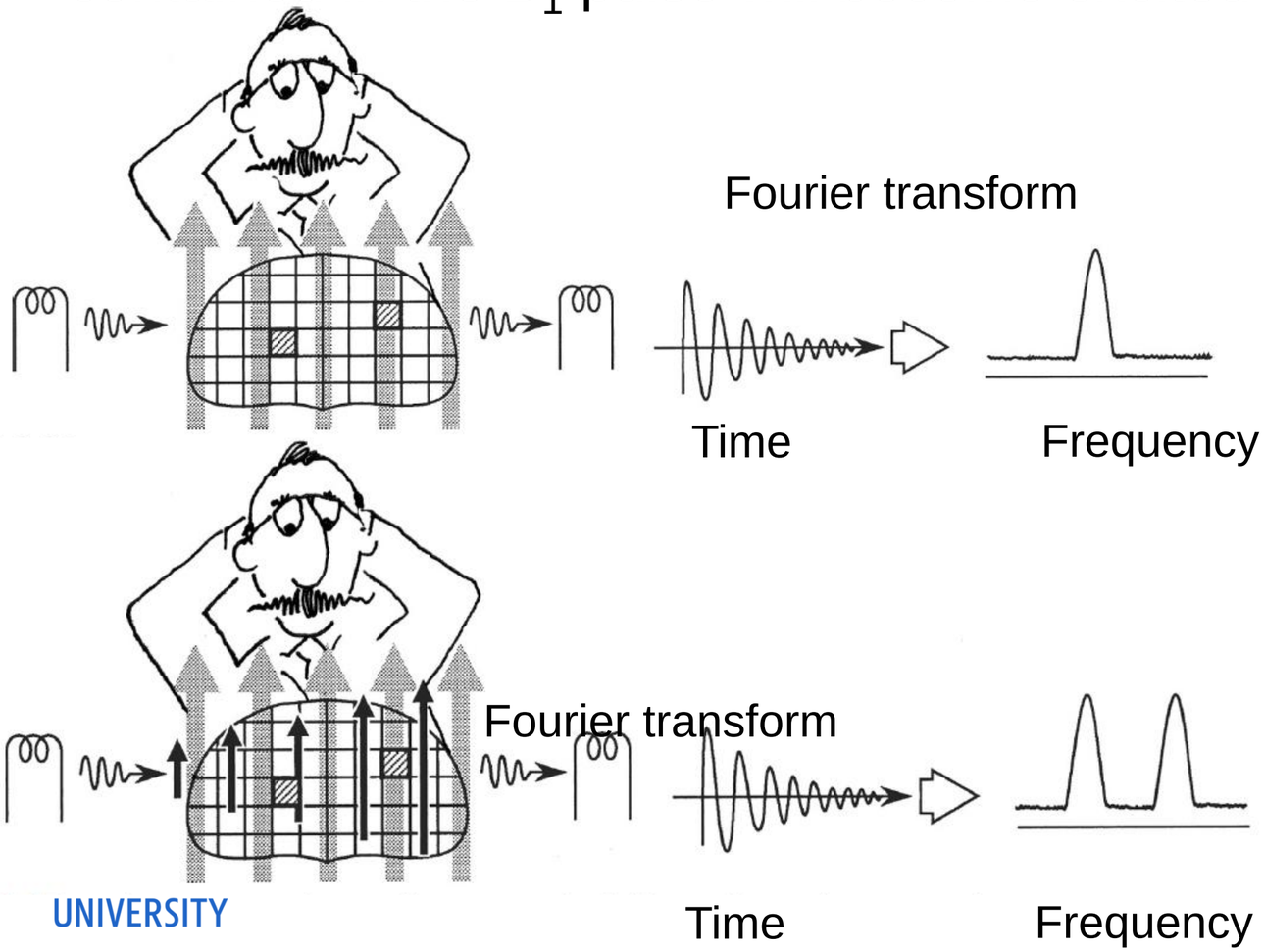
MAGNETIC RESONANCE IMAGING: IMAGING

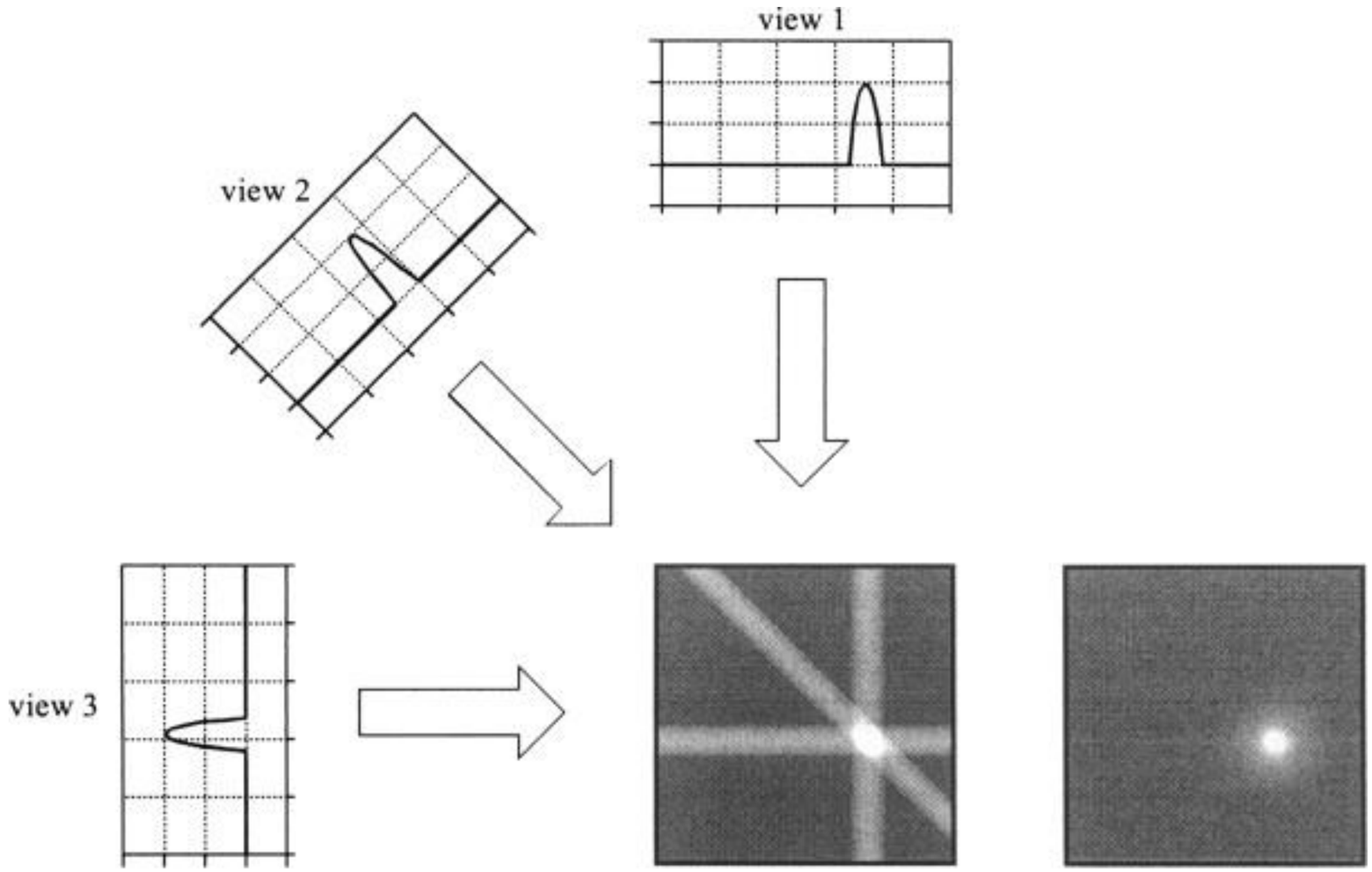
How to build an image? (very simple example)

make B_0 a function of position so that only nuclei precessing in the range of frequencies contained in the B_1 pulse will become excited



Projections can be obtained by rotating the gradient magnetic field around a patient. An image can be reconstructed from these projections by backprojection.

MAGNETIC RESONANCE IMAGING: IMAGING



a. Using 3 views

b. Using many views

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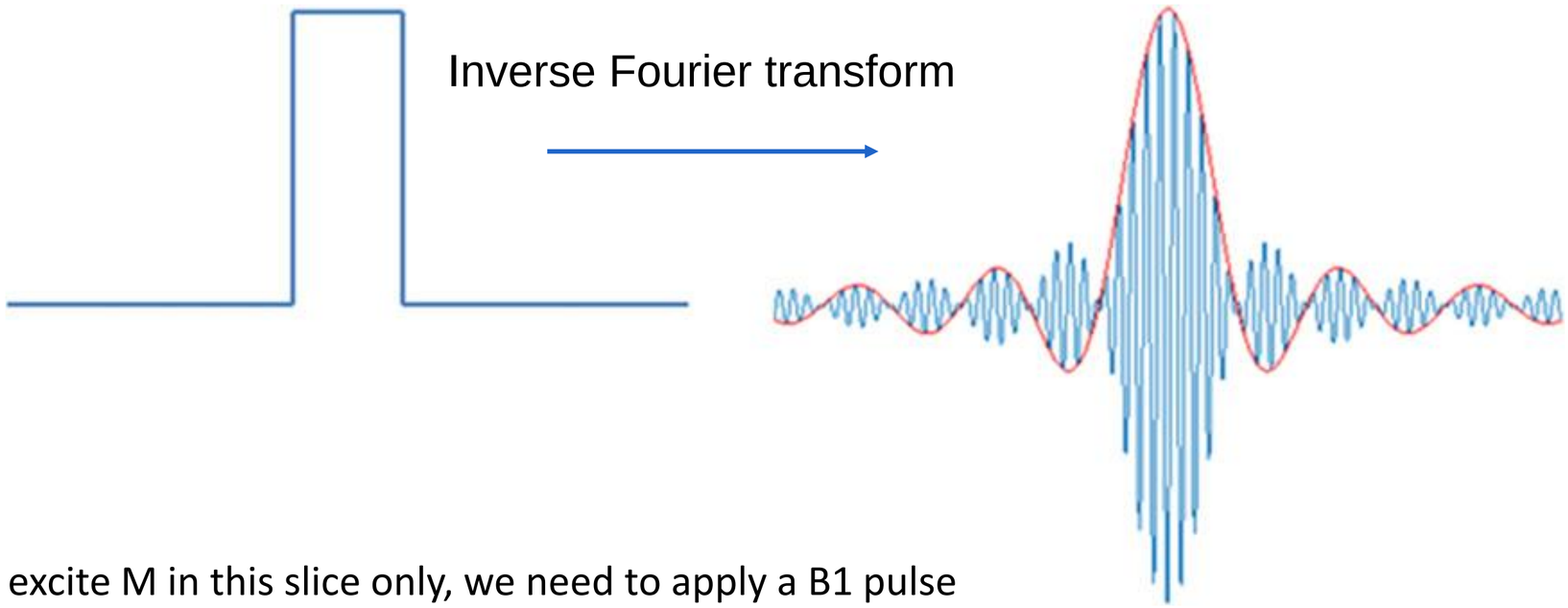
MAGNETIC RESONANCE IMAGING: IMAGING

assume that we want to map the signal from a single slice of tissue in a transverse or ‘axial’ plane—meaning a plane perpendicular to the axis of the B0 magnet, which is most often cylindrical in shape with the z-axis along its center. To accomplish this we can apply a z-oriented gradient such that $B_z = B_0 + zGz(t)$. For this example, let us suppose that B_0 is 1.5 T and Gz is 50 mT m^{-1} and we want to excite a 5 mm thick slice centered about z = 0

At what frequencies will the protons precess in this slice?

will precess at frequencies from about 63.8647 MHz to about 63.8753 MHz when the gradient is applied

What are the properties of B_1?



To excite M in this slice only, we need to apply a B1 pulse with a frequency centered at 63.87 MHz and having a bandwidth of about 10.6 kHz.

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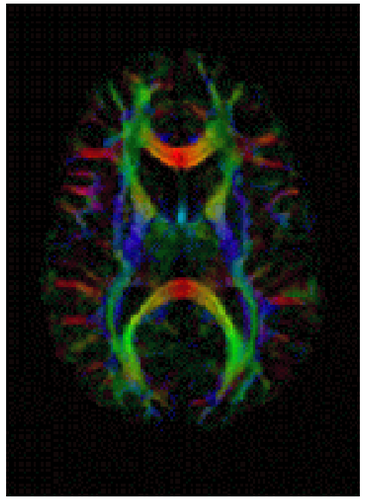
MAGNETIC RESONANCE IMAGING: APPLICATIONS



White matter tractography

- View of soft tissues due to change in relaxation, tumor detection, joint anomalies, spinal cord,abdominal images
- Functional MRI: map brain activity through magnetic difference between (de)/oxygenated blood
- Diffusion weighted imaging: mapping of the diffusion process of molecules, mainly water, in biological tissues. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture

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NEUROMAGNETISM

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NEUROMAGNETISM: INTRODUCTION

Electroencephalogram (EEG)

- Measures electrical activity of nerve cells
- Requires synchronous activity of large populations of cells to generate measurable signals
- EEG signals are modified considerably by the electrical properties of the head tissues

EEG yields excellent time (fractions of a millisecond), but poor spatial resolution

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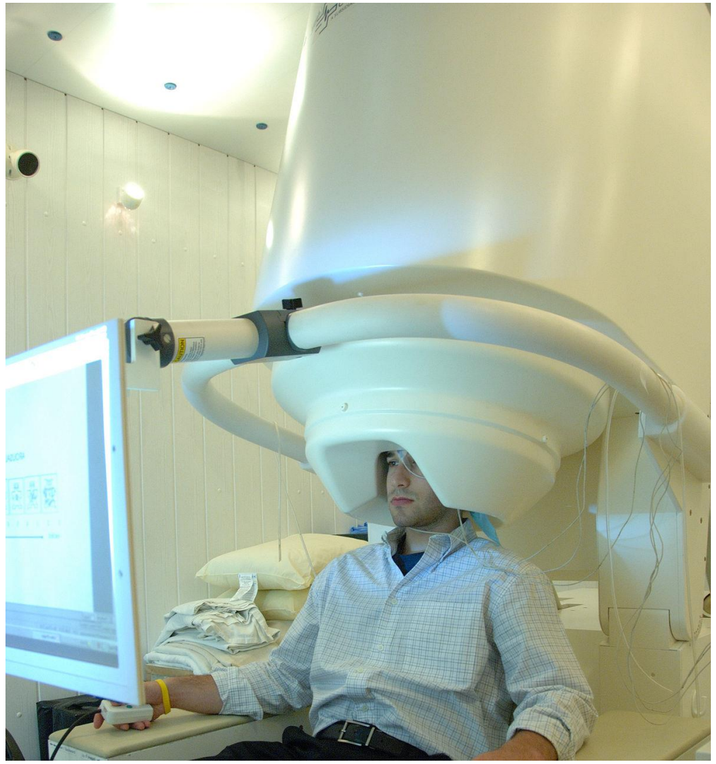
NEUROMAGNETISM: INTRODUCTION

Magnetoencephalogram (MEG)

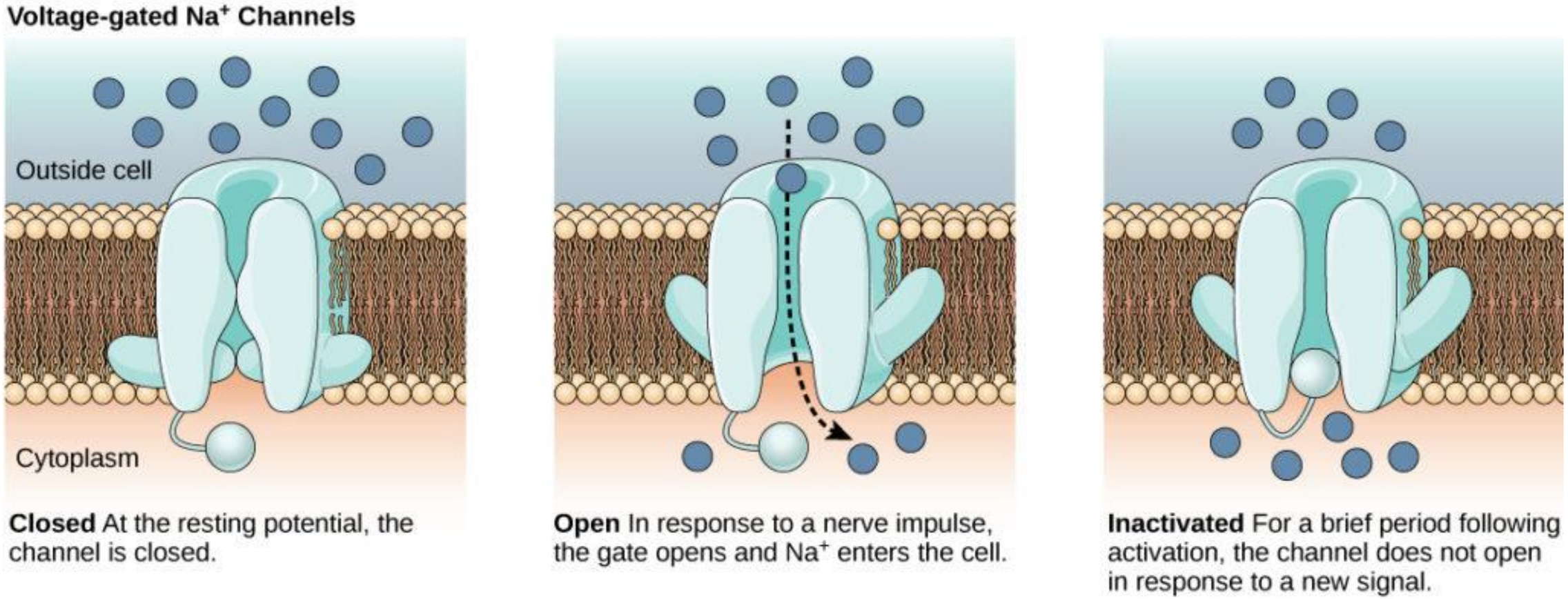


- Measures same activity as EEG
- Less disturbed by the complex conductivity profile of head -> higher spatial accuracy
- Extremely weak magnetic fields caused by neuronal electrical activity (~ 100 10^{-15}T) fT
- Magnetic shielding, gradiometers
- Direct measurement of currents (<->fMRI)

It is performed to map brain function and to identify the exact location of the source of epileptic seizures.

NEUROMAGNETISM: ORIGIN SIGNALS

– Ions form currents, membrane potential based on relative amounts of K^+ in and outside the cell



https://courses.lumenlearning.com/wm-biology2/chapter/resting-membrane-potential/

NEUROMAGNETISM: ORIGIN SIGNALS

Table 1. Ion Concentration Inside and Outside Neurons

Ion	Extracellular concentration (mM)	Intracellular concentration (mM)	Ratio outside/inside
Na^+	145	12	12
K+	4	155	0.026
Cl^-	120	4	30
Organic anions (A−)	—	100	

The resting membrane potential is a result of different concentrations inside and outside the cell. The difference in the number of positively charged potassium ions (K^+) inside and outside the cell dominates the resting membrane potential (Figure 2).

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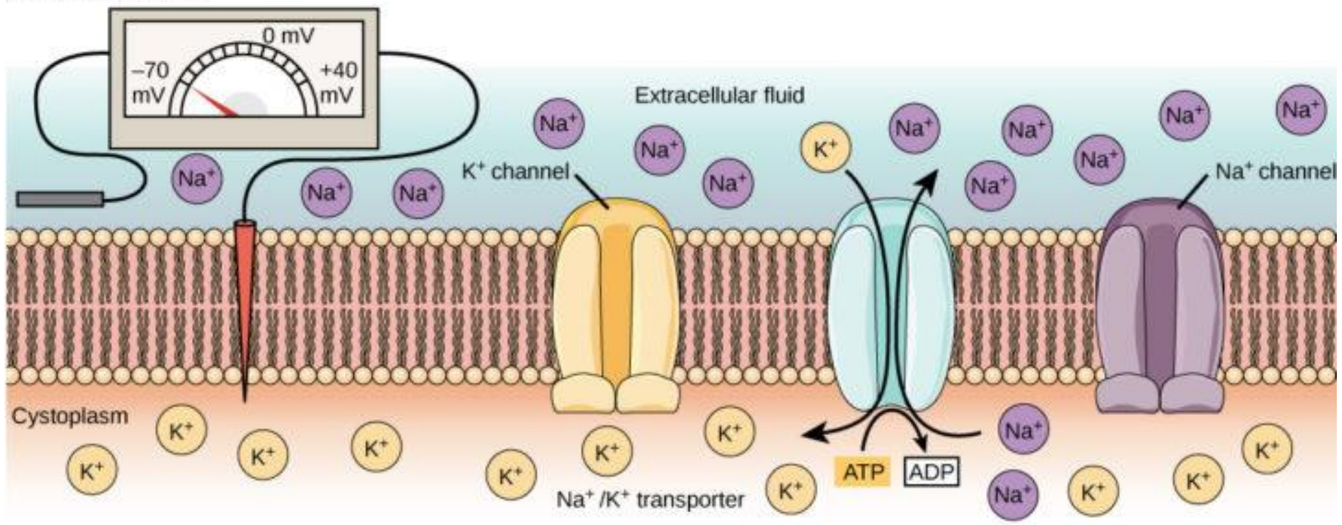
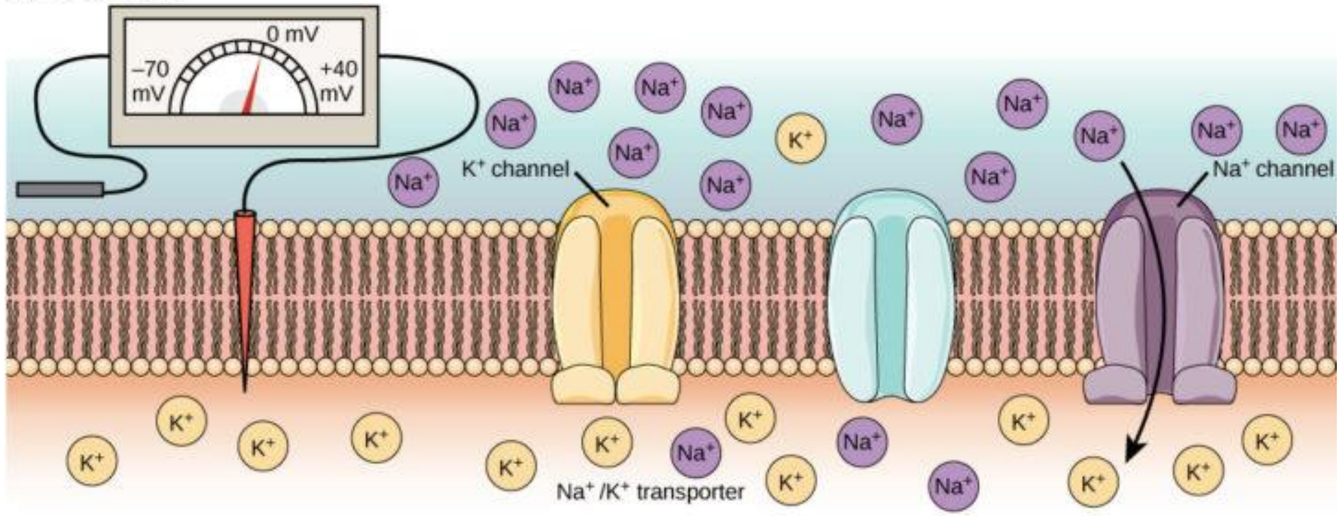
NEUROMAGNETISM: ORIGIN SIGNALS

(a) Resting potential



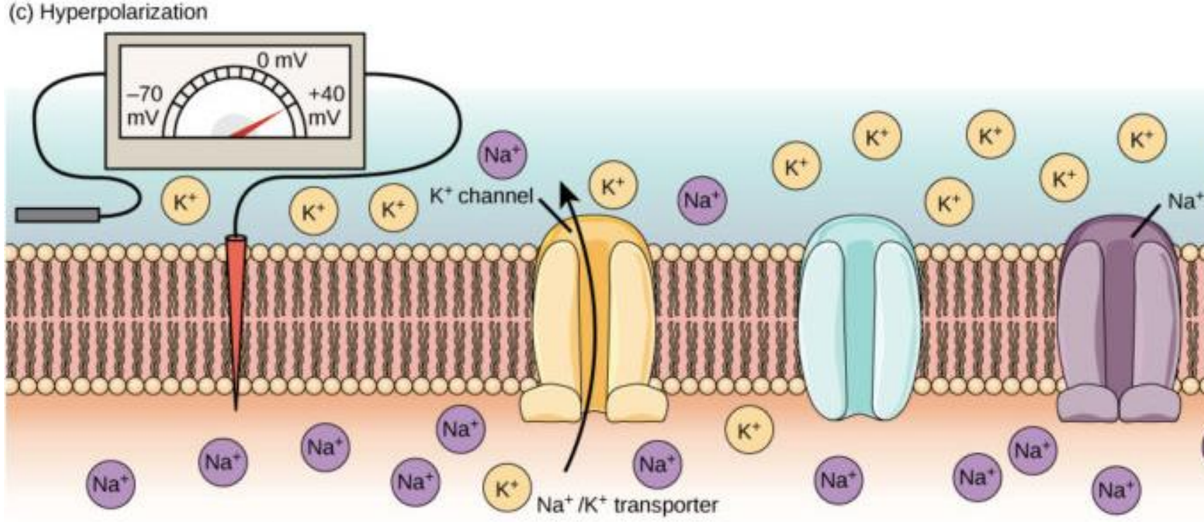
At the resting potential, all voltage-gated Na^+ channels and most voltage-gated K^+ channels are closed. The Na^+/K^+ transporter pumps K^+ ions into the cell and Na^+ ions out.

(b) Depolarization



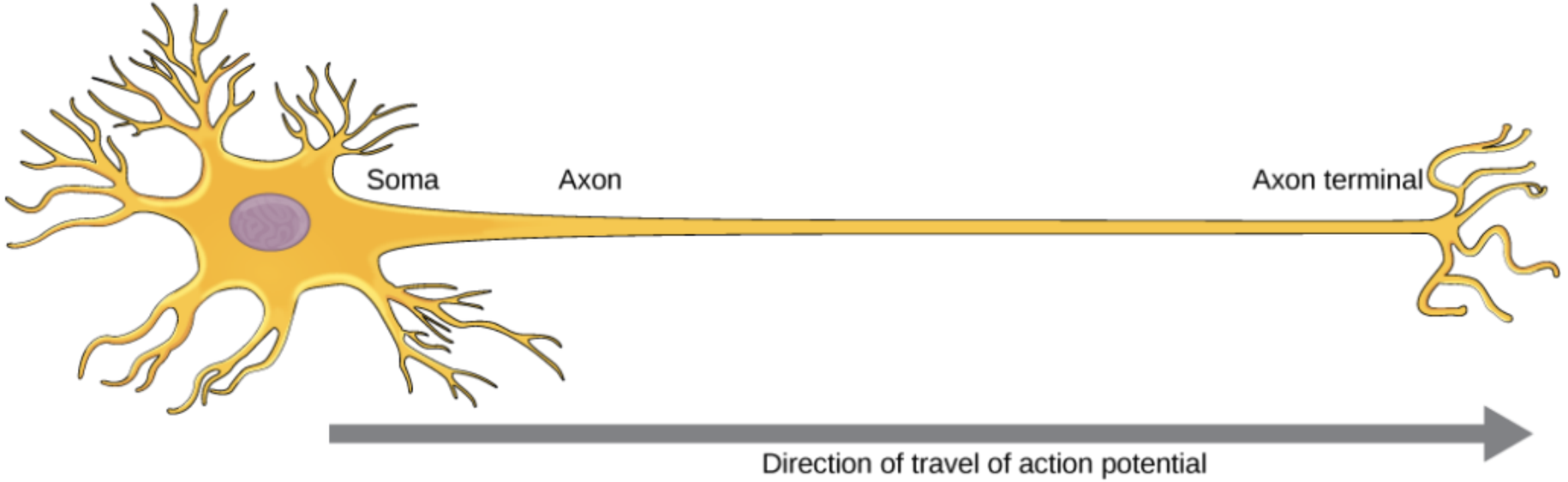
In response to a depolarization, some Na^+ channels open, allowing Na^+ ions to enter the cell. The membrane starts to depolarize (the charge across the membrane lessens). If the threshold of excitation is reached, all the Na^+ channels open.

(c) Hyperpolarization



At the peak action potential, Na^+ channels close while K^+ channels open. K^+ leaves the cell, and the membrane eventually becomes hyperpolarized.

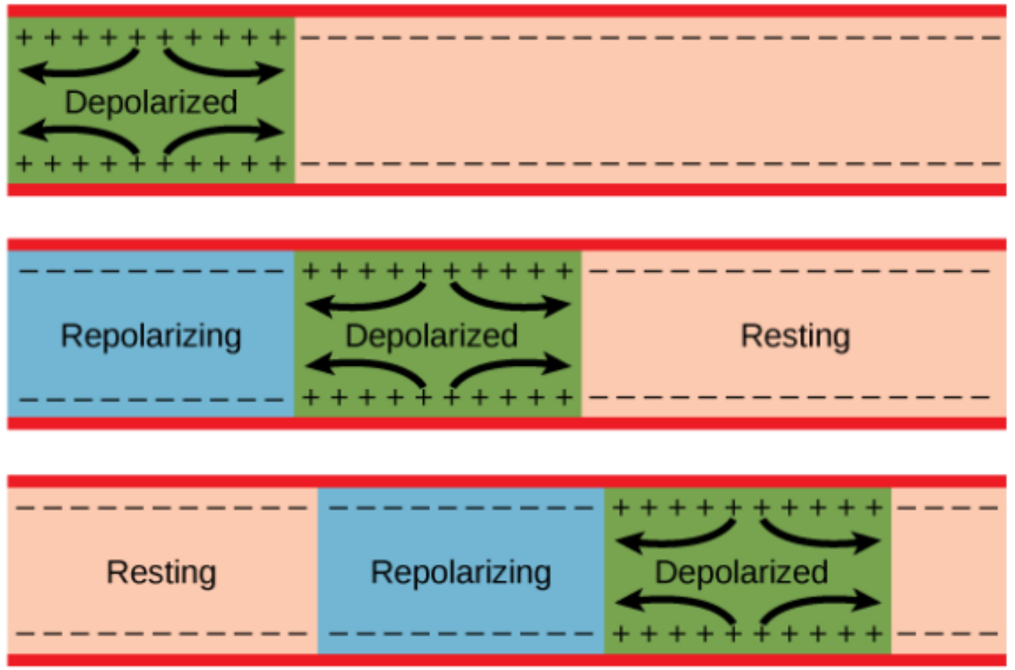
NEUROMAGNETISM: ORIGIN SIGNALS



a. In response to a signal, the soma end of the axon becomes depolarized.

b. The depolarization spreads down the axon. Meanwhile, the first part of the membrane repolarizes. Because Na^+ channels are inactivated and additional K^+ channels have opened, the membrane cannot depolarize again.

c. The action potential continues to travel down the axon.



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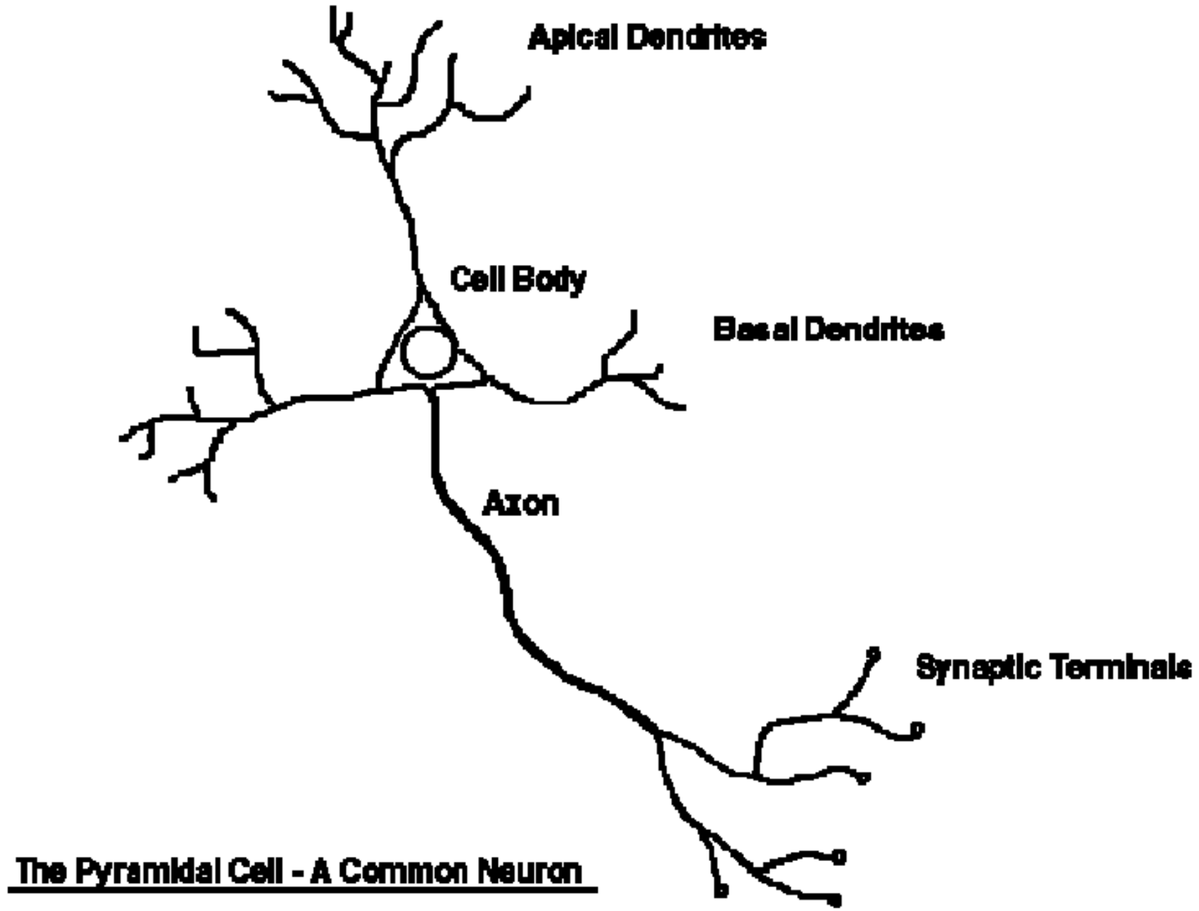
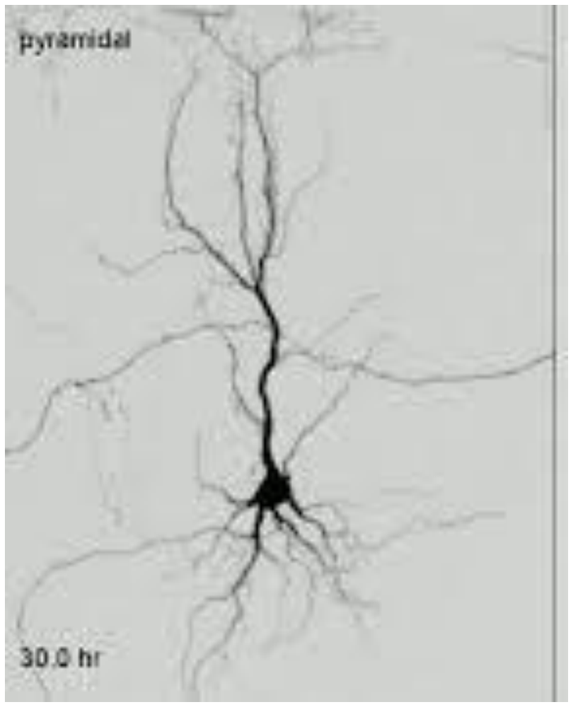
NEUROMAGNETISM: ORIGIN SIGNALS



Pyramidal cells are a good example of neurons with an open field structure (type I) generating magnetic fields detectable on the outside of the head



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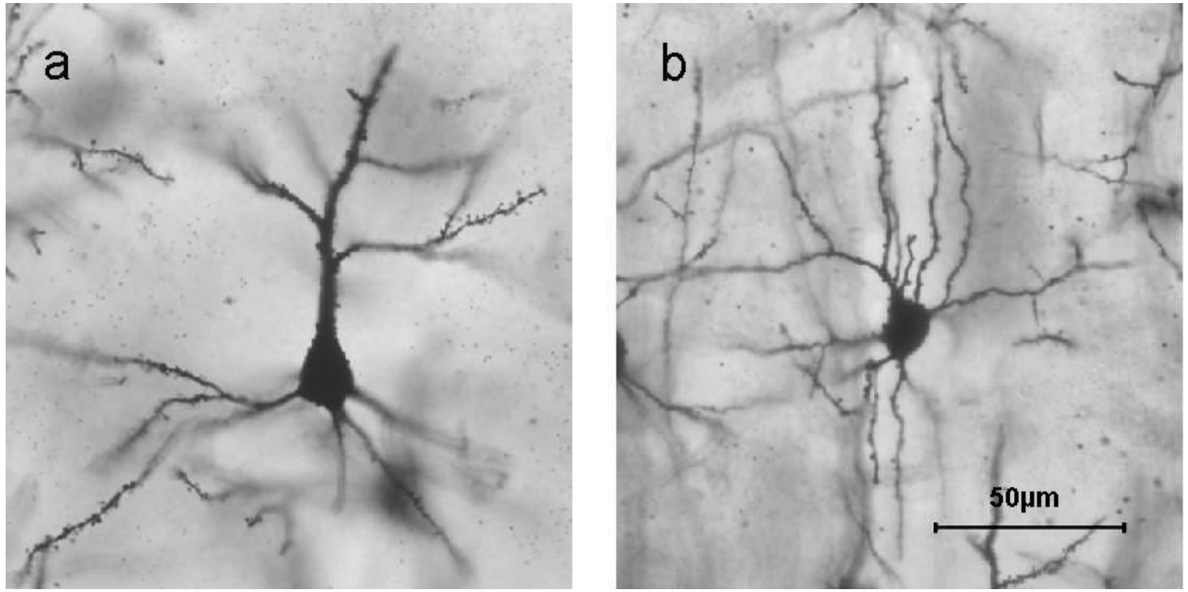
https://www.researchgate.net/profile/Weiliang-Chen-5/publication/228601970/figure/fig2/AS:669373823979520@1536602564046/Simplified-diagram-showing-the-structure-of-a-pyramidal-cell-The-neuron-is-divided-into.png

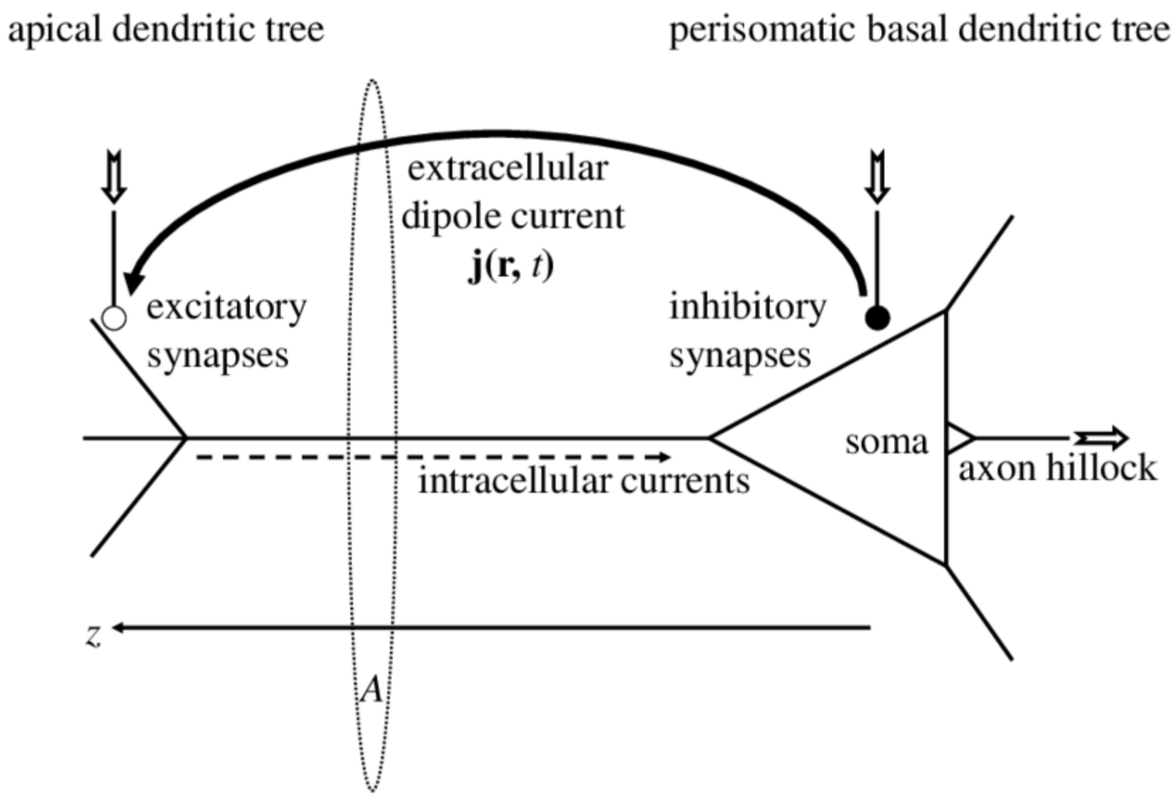
NEUROMAGNETISM: ORIGIN SIGNALS

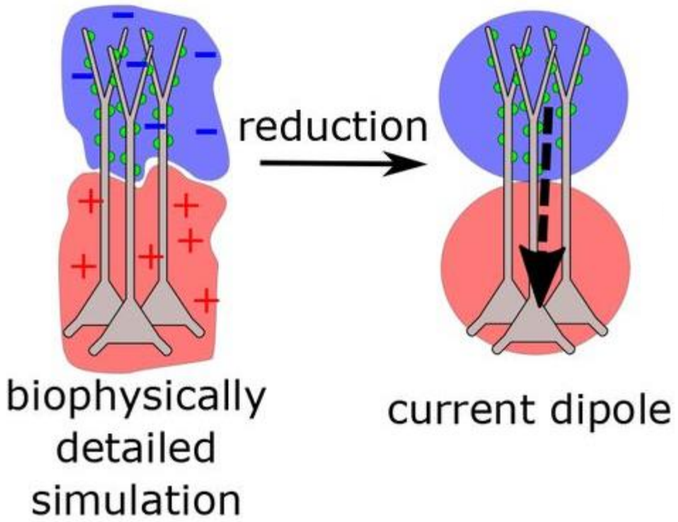


At the other extreme is the cell of which the dendrites extend radially in all directions. This type is said to have a “closed field” configuration, because field potential changes are limited to the length of the dendrites. In a cell with a closed-field configuration with major activation of its dendrites, the current is radially symmetric (spherical symmetry). No magnetic field can be detected. The stellate cell may be considered the ideal neuron with a closed-field configuration.

NEUROMAGNETISM: CURRENT DIPOLE

The working of a single neuron can be modelled as a current dipole, which generates a small amount of electrical. A large simultaneously active group of neurons produces thus a current dipole, which produces a magnetic field outside the human head that can be picked up by the SQUID sensors





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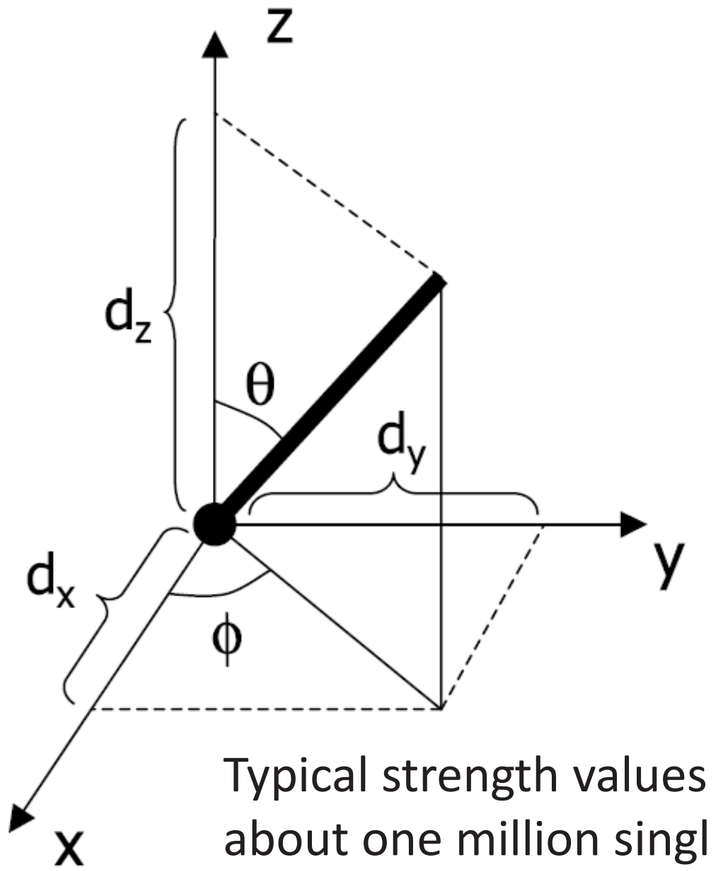
NEUROMAGNETISM: CURRENT DIPOLE

Current dipole is characterized by 6 parameters, 3 for position, 2 for direction and 1 magnitude of the dipole



A current dipole adequately describes the current flow in a small volume element (‘‘small’’ as compared to the distance between sources and sensors)

Typical strength values are around 20 nAm, accounting for about one million single postsynaptic potentials

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NEUROMAGNETISM: BIOT SAVART LAW

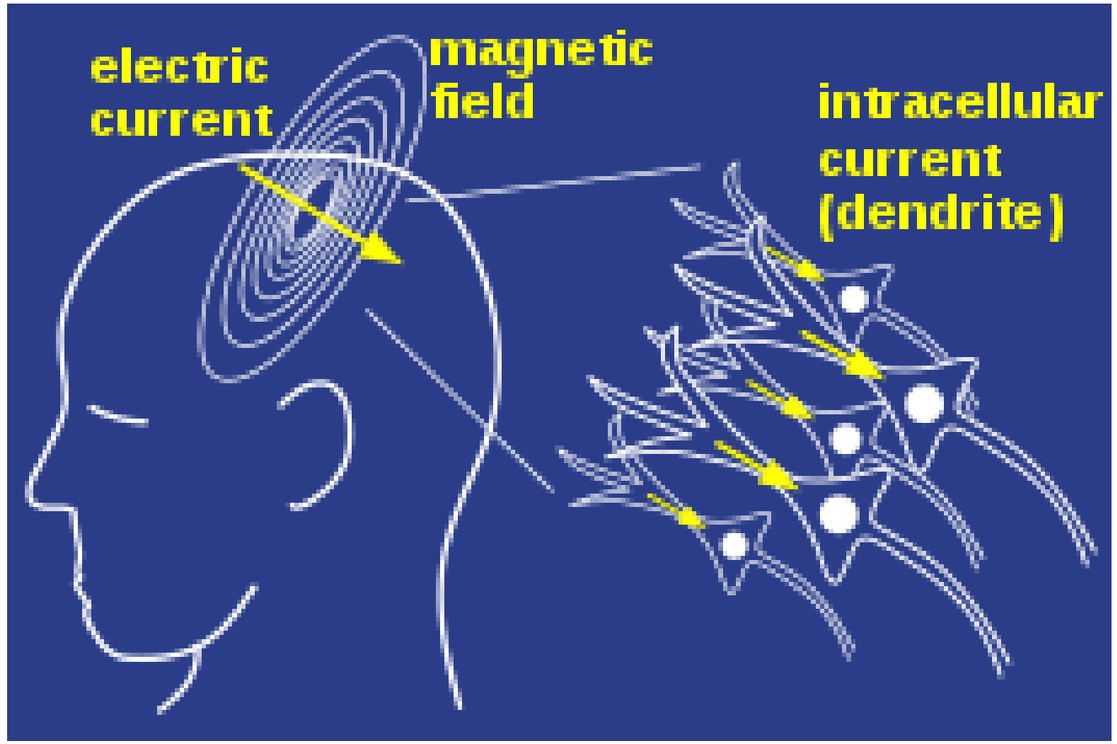
- Neural activity has a low frequency
Maxwell's equations -> quasistatic approximation
(i.e. inductive and capacitive effects
can be neglected) Biot-Savart law

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int \mathbf{J}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} d^3 r'$$

$\mathbf{J}(\mathbf{r}')$ = dipole moment (strength, orientation), r' location dipole, r location sensor

μ_0 = vacuum permeability, B is magnetic induction

– Magnetic field decays ~$1/r^3$



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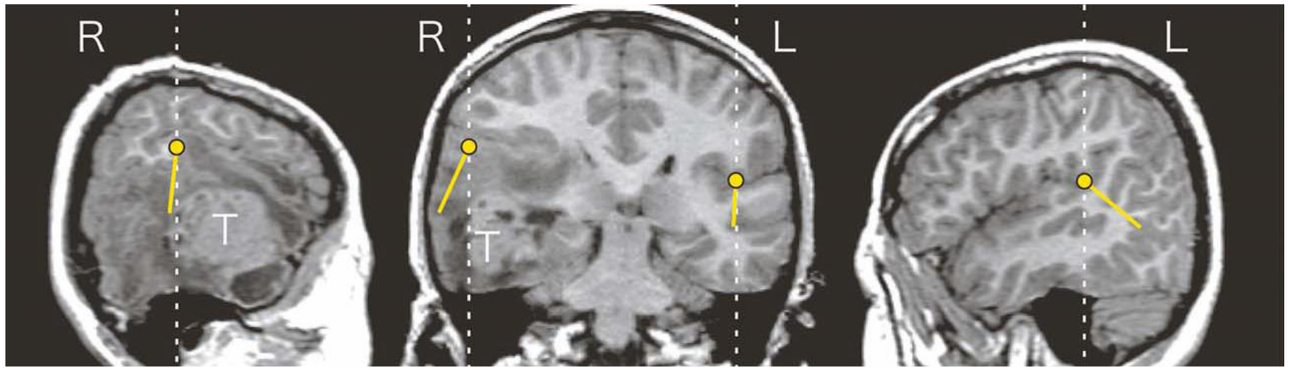
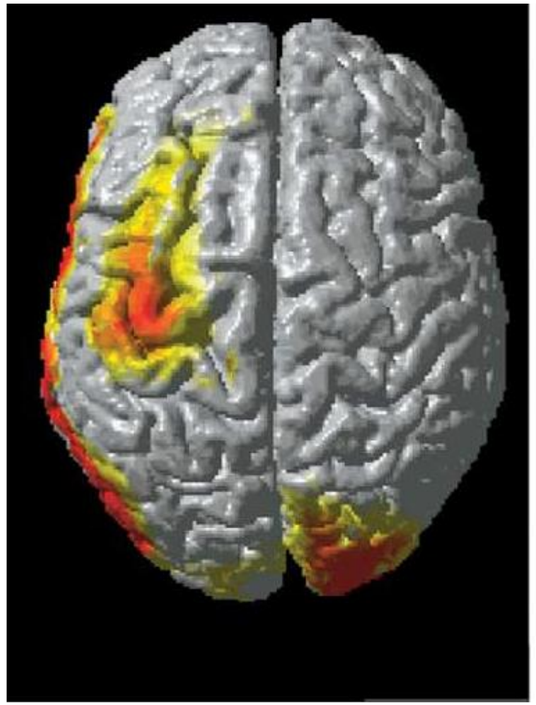
NEUROMAGNETISM: SOURCE MODEL

Focal activity such as an epileptic seizure, auditory evoked signal, can be modeled with a single or a few dipoles





More complex source configurations can be described as a linear combination of many dipolar elements. By increasing the number of dipolar elements, one can in principle reach any level of accuracy.

$$\vec{B}_{\infty}(\vec{r}) = \frac{\mu_0}{4\pi} \sum_{i=1}^{N} \frac{\vec{q}_i \times (\vec{r} - \vec{r}_{q_i})}{|\vec{r} - \vec{r}_{q_i}|^3}$$

B is magnetic induction, N is the number of dipoles, q_i is the moment of the ith current dipole, r is the location of measurement, and r_{qi} the location of ith dipole.

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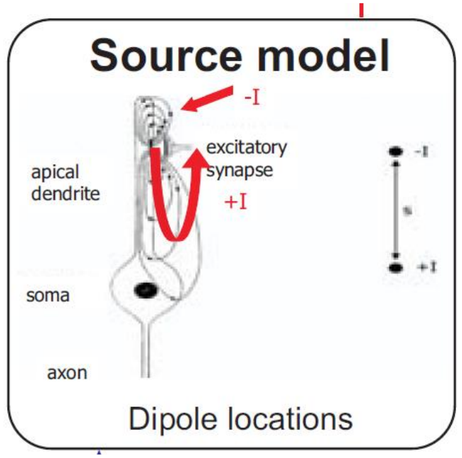
NEUROMAGNETISM: NEUROELECTROMAGNETIC INVERSE PROBLEM

Brain signals obtained with MEG contain information on the spatial distribution of the underlying generators throughout the brain, though the information is incomplete.

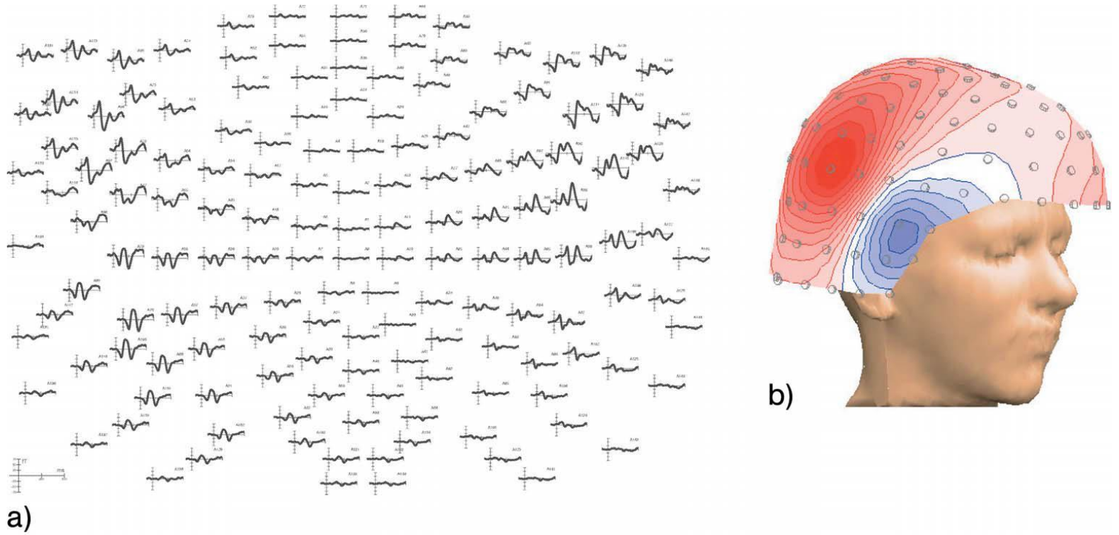
→ Extract information by solving the neuroelectromagnetic inverse problem

Two sub-problems the *forward model* and the *inverse problem*

Forward model



Unique solution



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The solution of the neuroelectromagnetic forward problem simulates MEG signals, given a certain set of neuronal generators (sources) as well as certain physical properties of the surrounding head tissue and the measurement apparatus

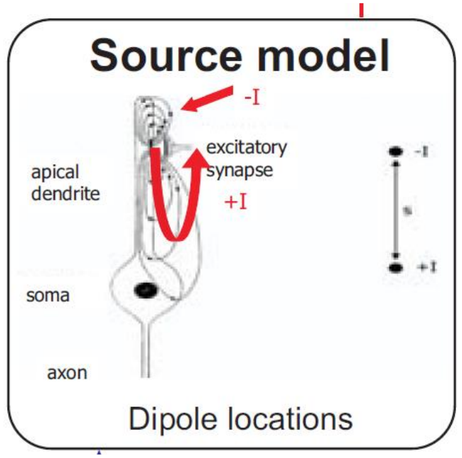
NEUROMAGNETISM: NEUROELECTROMAGNETIC INVERSE PROBLEM

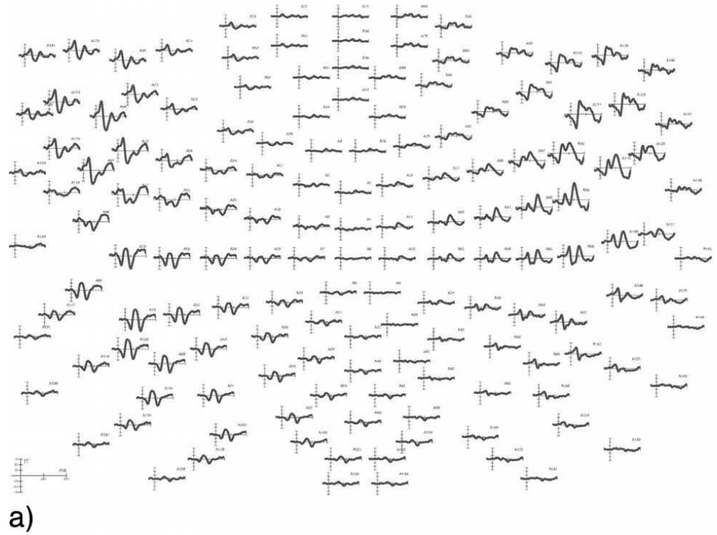
Brain signals obtained with MEG contain information on the spatial distribution of the underlying generators throughout the brain, though the information is incomplete.

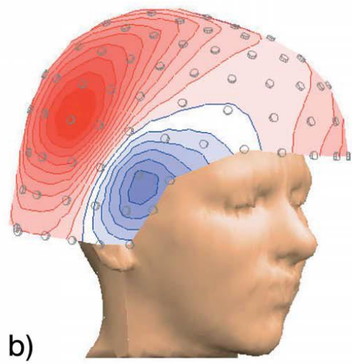
→ Extract information by solving the neuroelectromagnetic inverse problem

Two sub-problems the *forward model* and the *inverse problem*

Inverse problem







The solution of the inverse problem is based on the forward solution and attempts to reconstruct the sources from the actually measured signals.

NEUROMAGNETISM: UNDERDETERMINED INVERSE PROBLEM

For any given set MEG measurements, there are an infinite number of possible source configurations that could have given rise to these signals, no matter how many sensors we use and how accurately we measure. So, which of these solutions should be preferred?

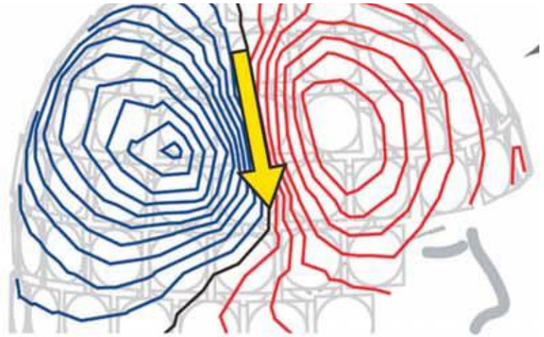
Occam's razor and *Bayes' law on conditional probabilities*

The law of Bayes: incorporate additional knowledge, for example from other imaging modalities (e.g., fMRI, simultaneous recording with EEG,…) or from anatomical constraints, thus reducing the degree of underdetermination of the inverse problem.

Occam's razor: from all equally probable solutions the simplest one should be preferred -> reduce number of dipoles

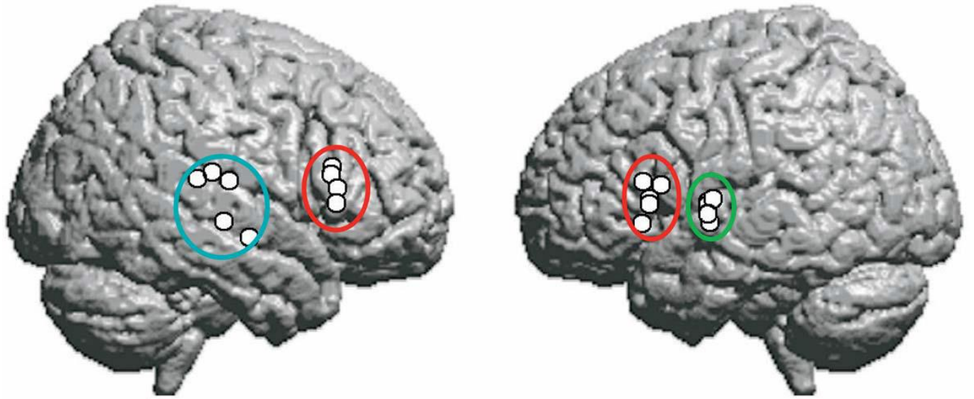
NEUROMAGNETISM: SOURCE MODEL

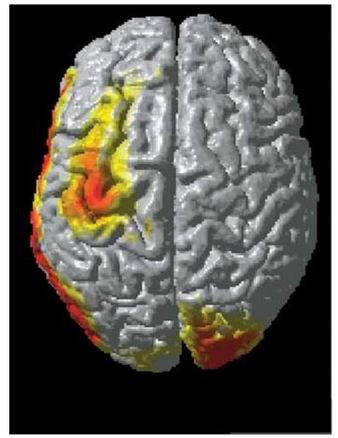
spatio-temporal multiple dipole model: the time courses, positions, and orientations of two or three current dipoles



- *moving dipole model* imposes no constraints – the strengths, orientations, and positions are independent between different latencies
- *fixed dipole model* positions and orientations remain constant over the entire period of analysis, while only the strengths may change
- *rotating dipole model* stationary dipole positions, but time-variant orientations

*distributed current source density distribution: P*redefined region of interest is discretized into suitably small elements, each of which is characterized by a set of two or three current dipoles. The positions of these dipoles are fixed to the element center, while their orientations are chosen in such a way that they span the space of possible current flow directions only currents tangential to the brain surface (MEG)





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MAGNETIC STIMULATION

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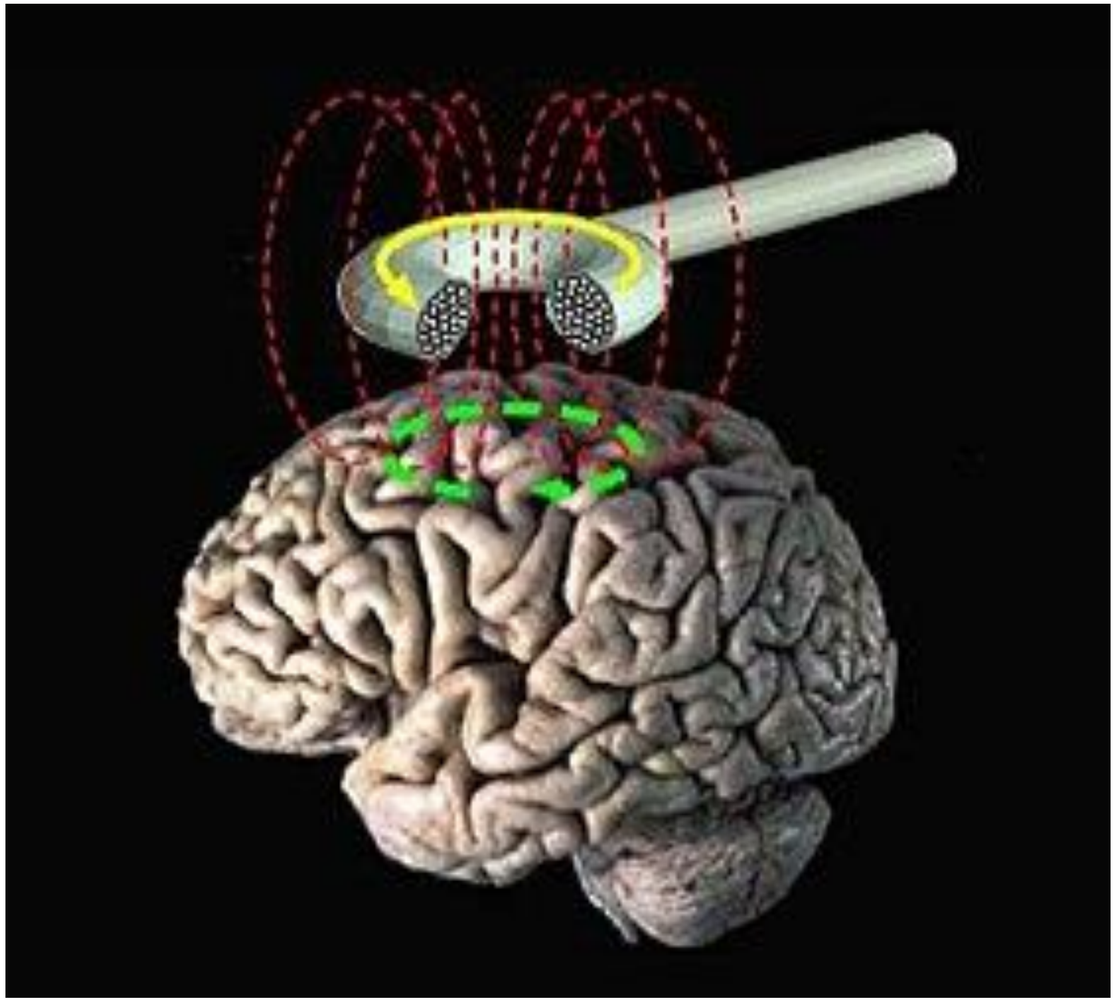
MAGNETIC STIMULATION: INTRODUCTION

Uses magnetic fields to stimulate nerve cells e.g. to reduce pain, depression, treatment of aphasia

Sub-millisecond high current (up to 10kA) pulse generates time-varying magnetic field which induces eddy current in the brain

Effects vary based on frequency and intensity of the magnetic pulses as well as the length of the pulse train

First human brain magnetic stimulation mid 1980s



https://upload.wikimedia.org/wikipedia/commons/6/67/Transcranial_magnetic_stimulation.jpg

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MAGNETIC STIMULATION: COIL TYPES

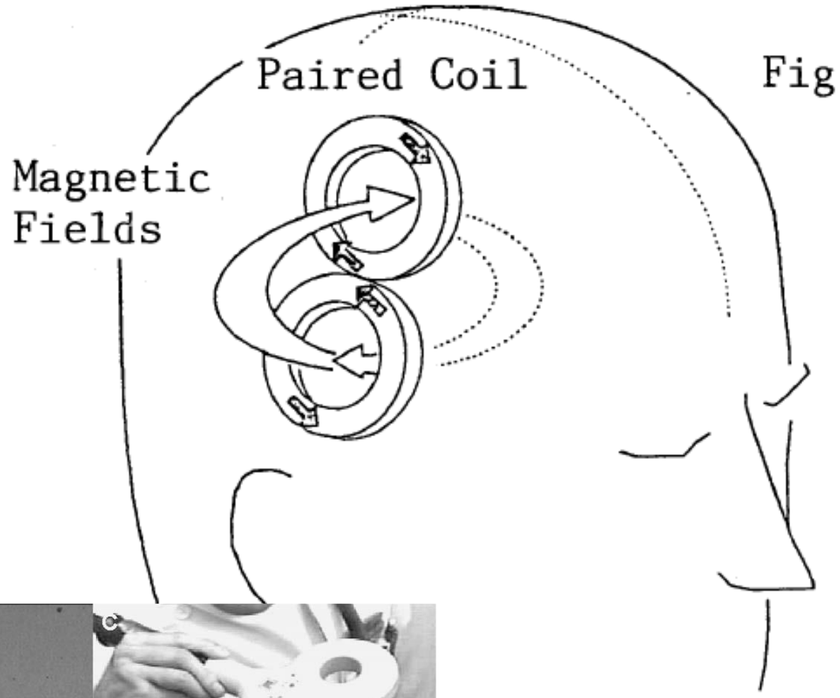
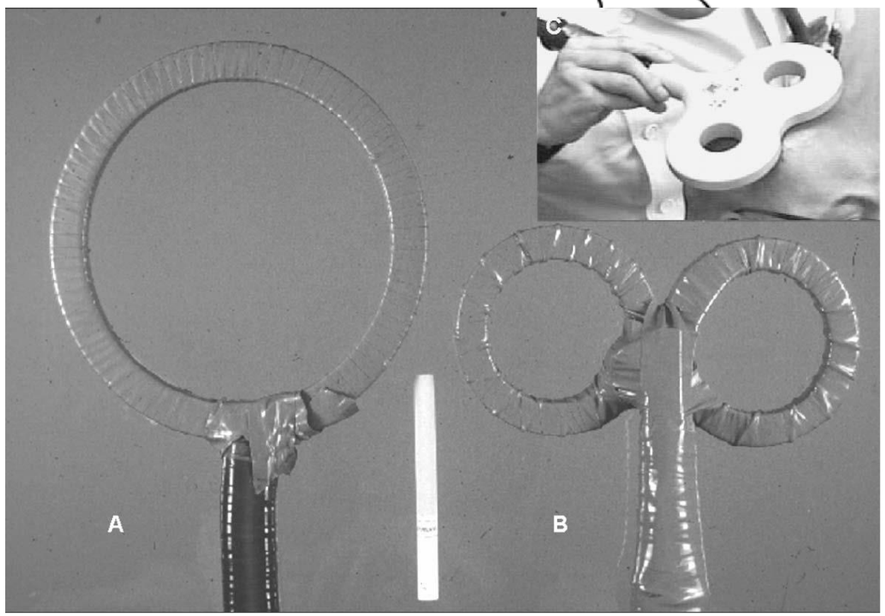
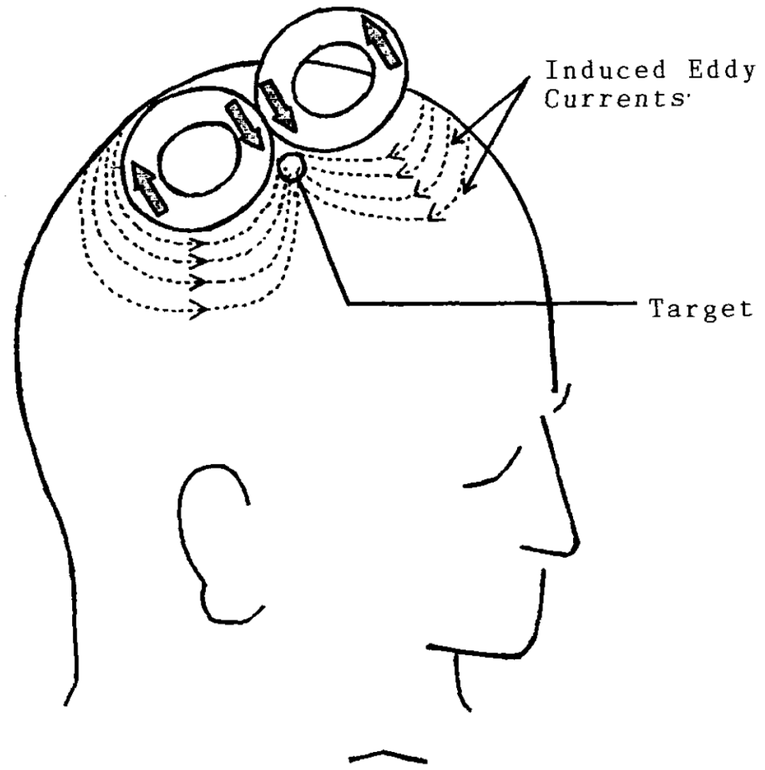
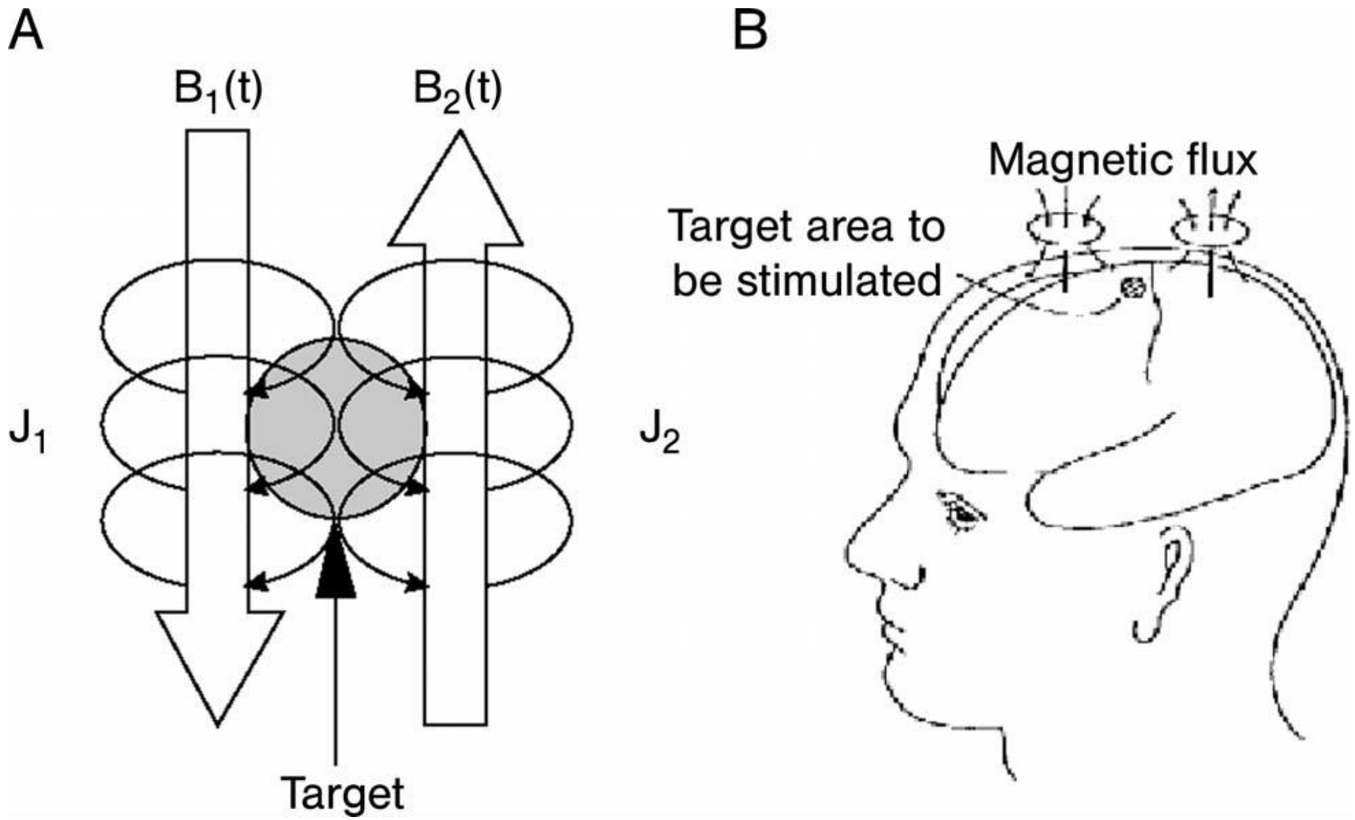


Fig.1 Principle of localized stimulation of the brain. A pair of coils are positioned outside the head so that magnetic fields path through the head in the opposite directions around a target which is located beneath the cross point of the paired coil.





MAGNETIC STIMULATION: WORKING PRINCIPLE



A pair of coils is positioned outside the head so that the time-varying magnetic fields, $B_1(t)$ and $B_2(t)$, enter the head in opposite directions close to the target. The induced eddy currents, J_1 and J_2, are expected to flow together. This convergence of eddy currents acts to raise the current densities in the target area, where depolarization of neural tissues can be caused

MAGNETIC STIMULATION: FUNCTIONAL MAP

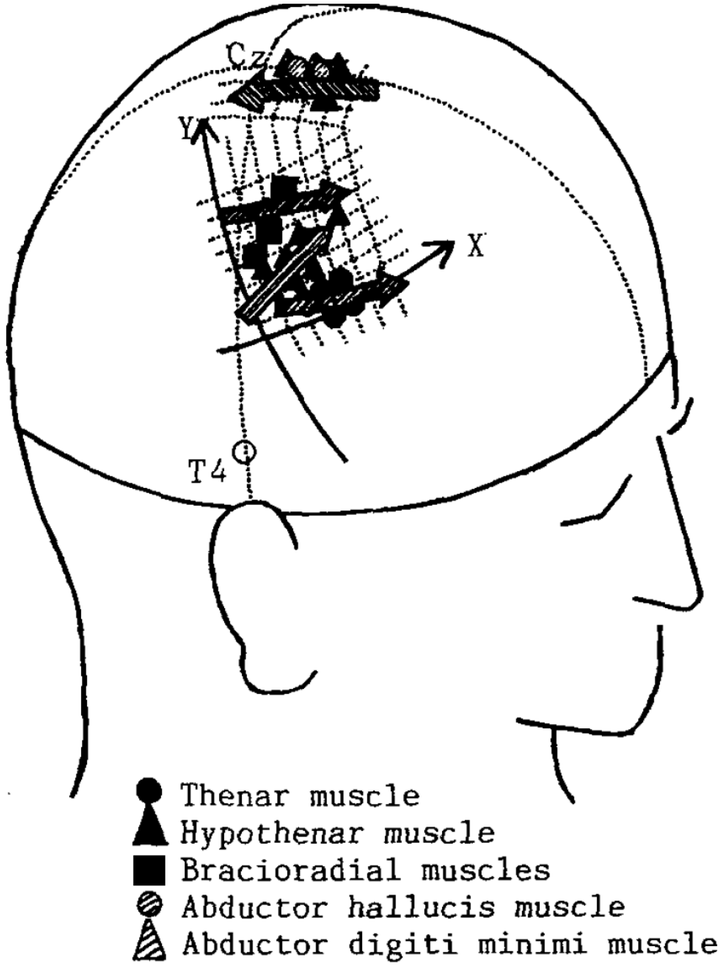
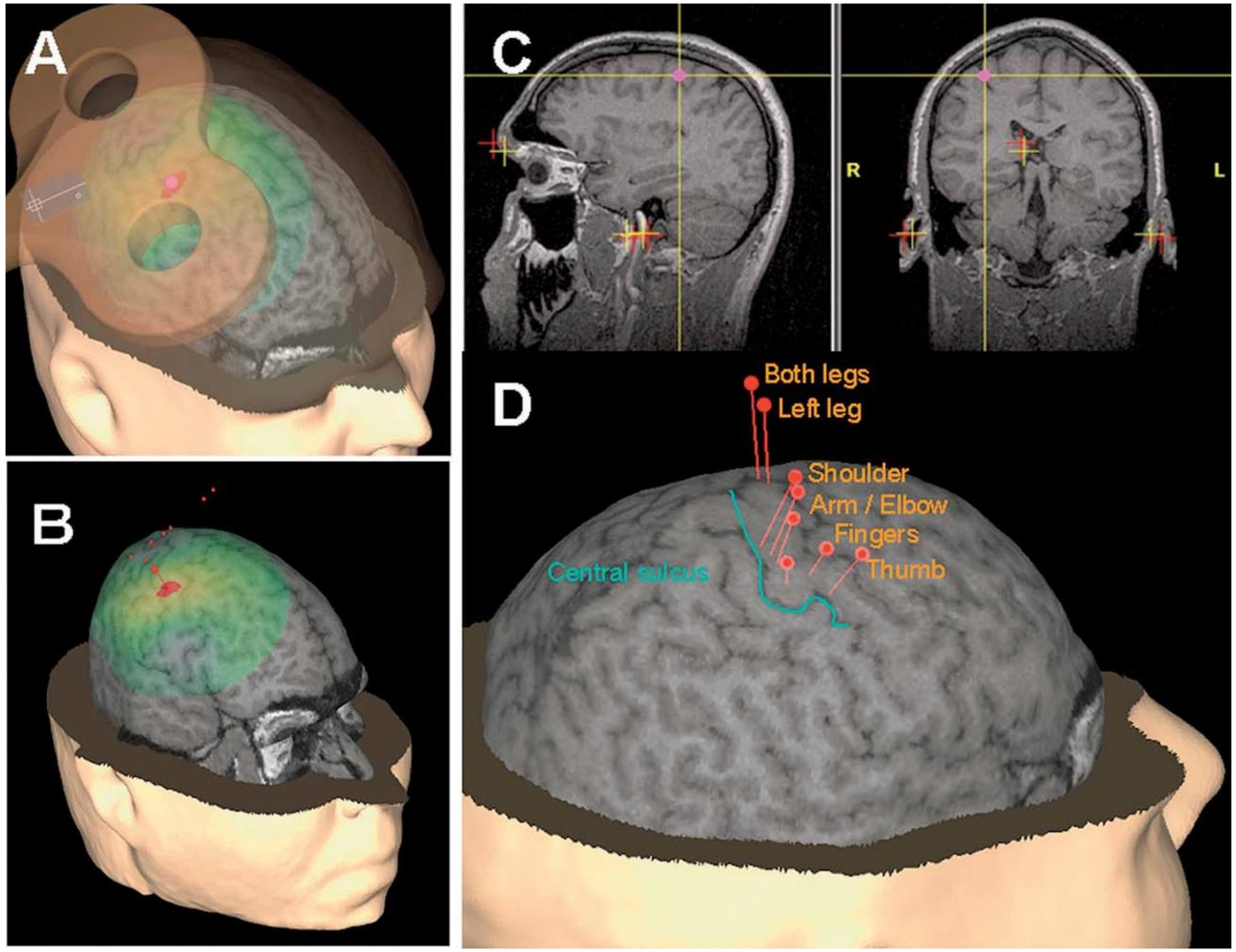


Fig.5 Functional distribution of the human motor cortex related to the hand and foot areas. The arrows show current directions for neural excitation. The distance between grid points is 5 mm.



optimal direction of stimulating currents for neural excitation exists in each functional area in the cortex

BIOMEDICAL APPLICATIONS OF MAGNETIC NANOPARTICLES

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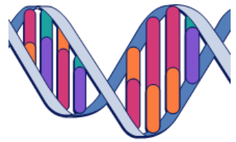
MAGNETIC NANOPARTICLES: STRUCTURE

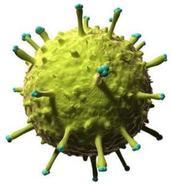
Molecules

Genes

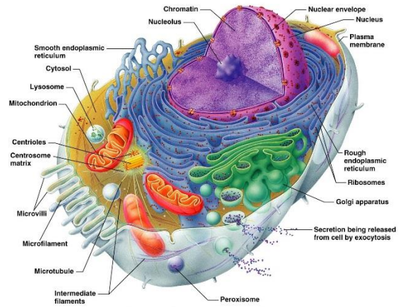


Proteins

Viruses



Magnetic nanoparticles



Cells

0.1 nm | 1 nm | 10 nm | 100 nm | 1 µm | 10 µm | 100 µm

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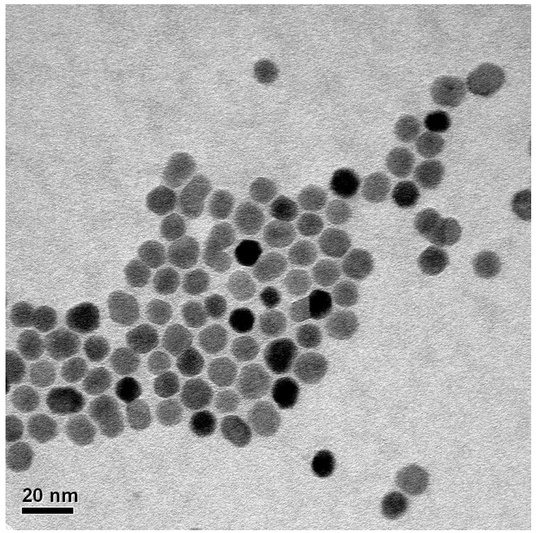
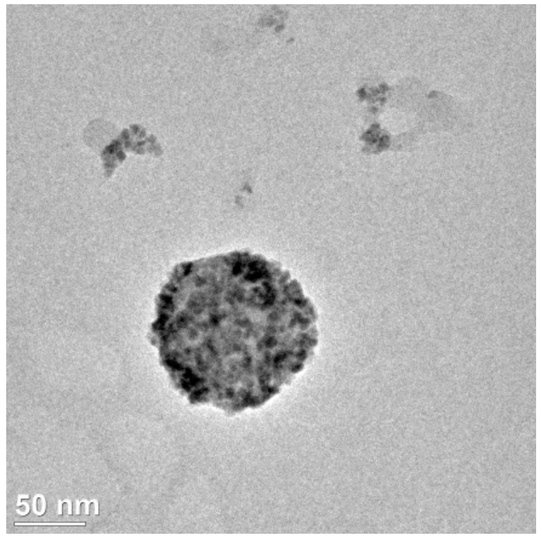
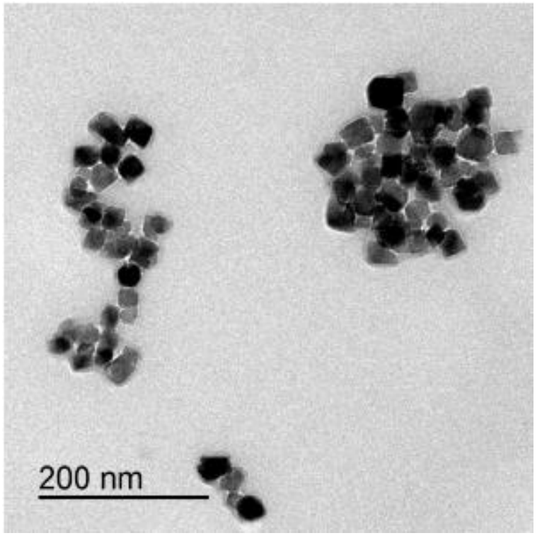
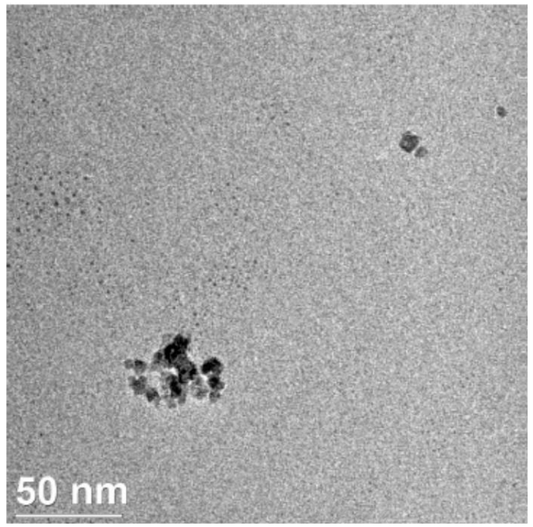
MAGNETIC NANOPARTICLES: STRUCTURE

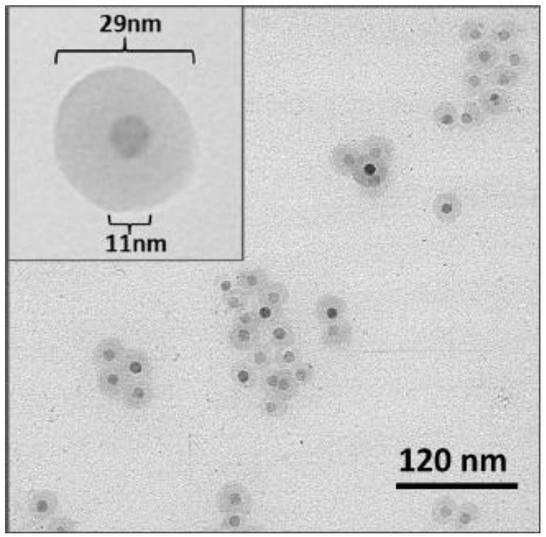
Various shapes and sizes

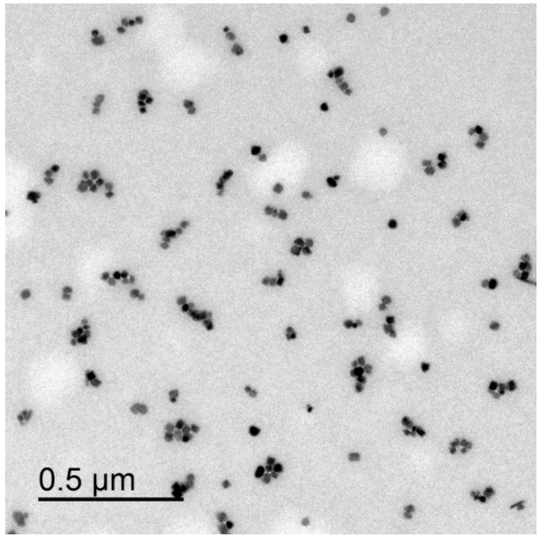












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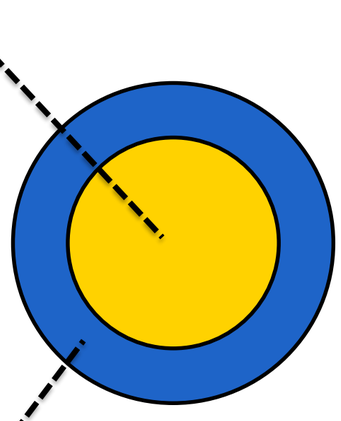
MAGNETIC NANOPARTICLES: STRUCTURE

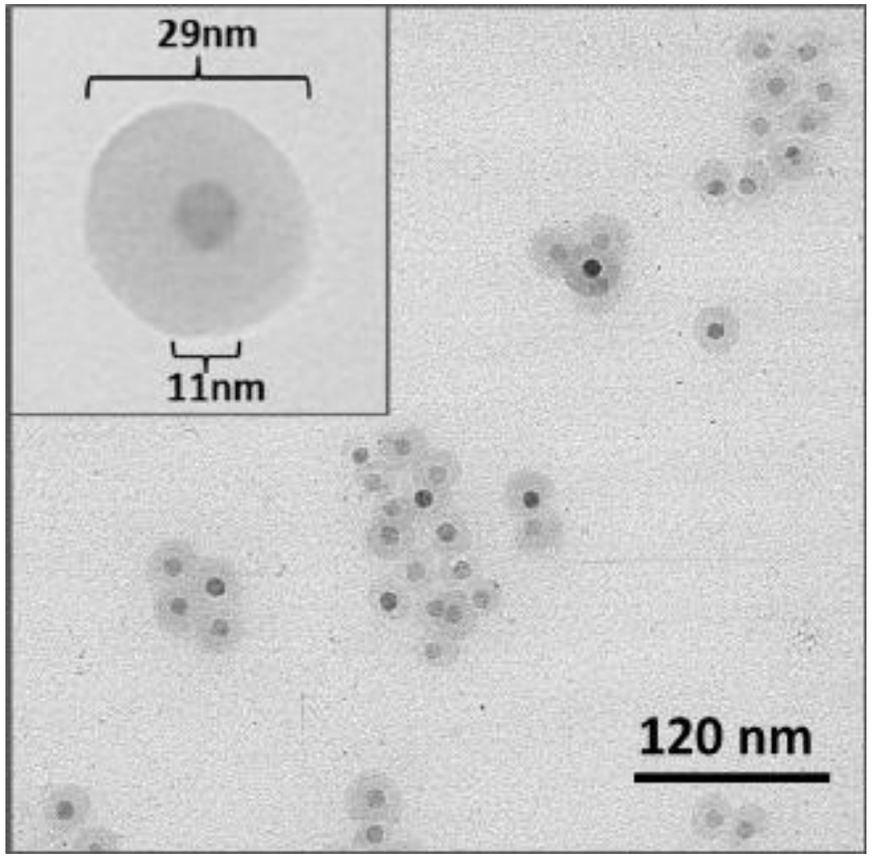
magnetic core ⟷

- Non-invasive detection
- Remotely controllable
- Dynamic response to magnetic fields



coating ⟷

- Biocompatible
- Interaction particles
- Functionalized



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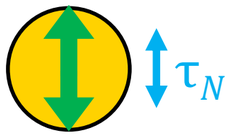
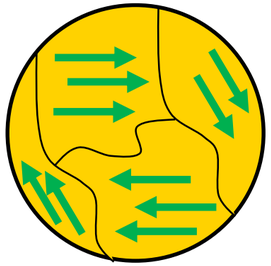
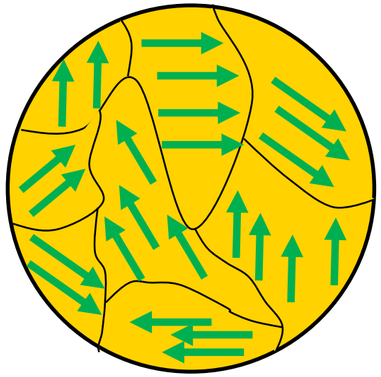
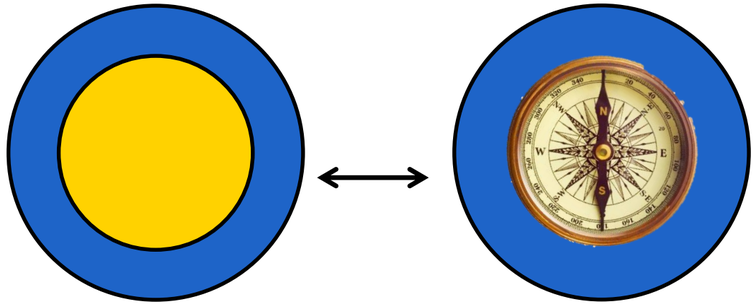
MAGNETIC NANOPARTICLES: MAGNETIC PROPERTIES

Magnetization response particles in external magnetic field depends on magnetic material and size particle







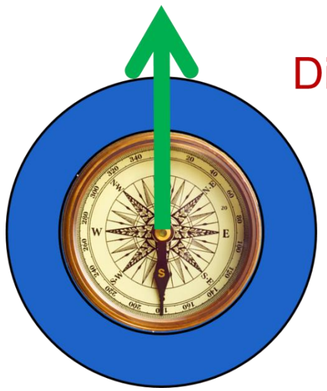


Superparamagnetic nanoparticle

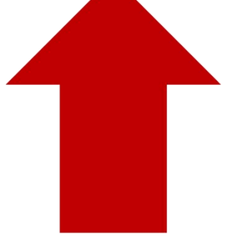
Single-domain nanoparticle

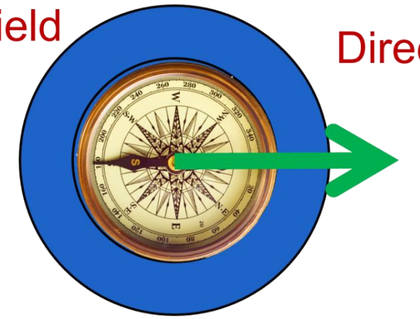
Multi-domain nanoparticle

Multi-domain nanoparticle

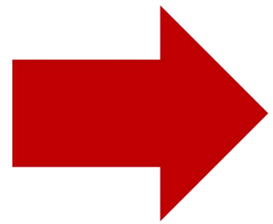


Direction magnetic field





Direction magnetic field



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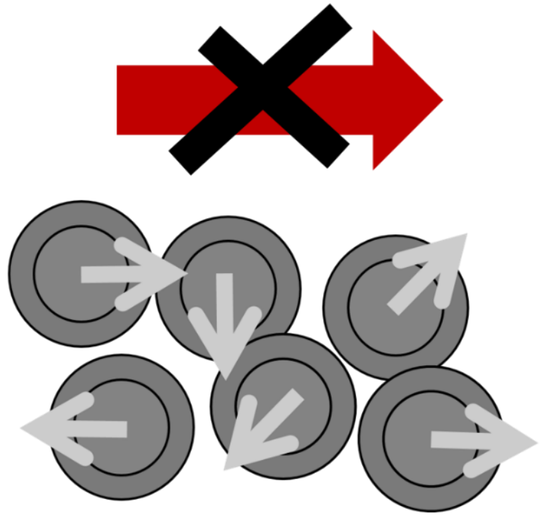
MAGNETIC NANOPARTICLES: MAGNETIC PROPERTIES

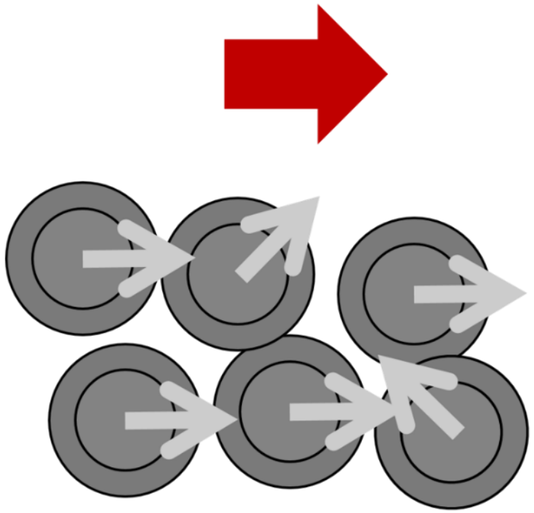
Magnetic response of *ensemble* of magnetic nanoparticles

No magnetic field

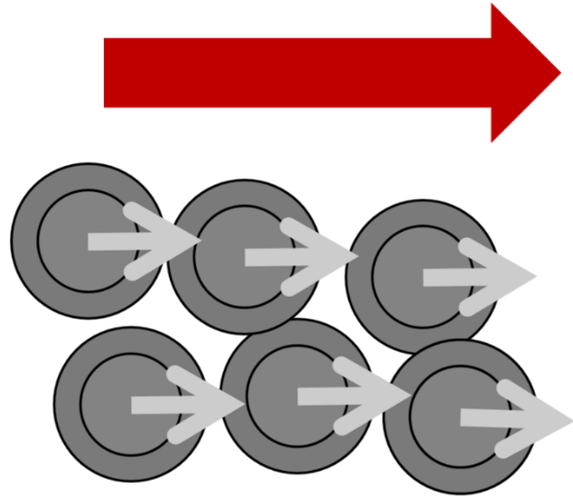


Random orientation particles

Magnetic field H

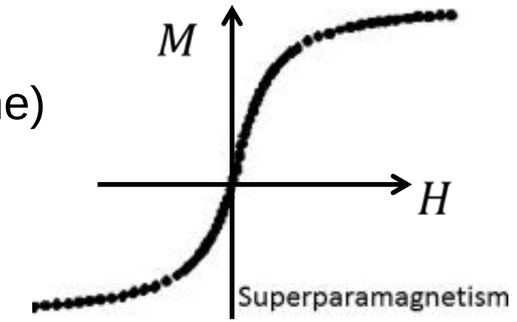


Larger magnetic field H



$$\mathbf{M} = \chi_0 \mathbf{H}$$

(In quasi-static regime)



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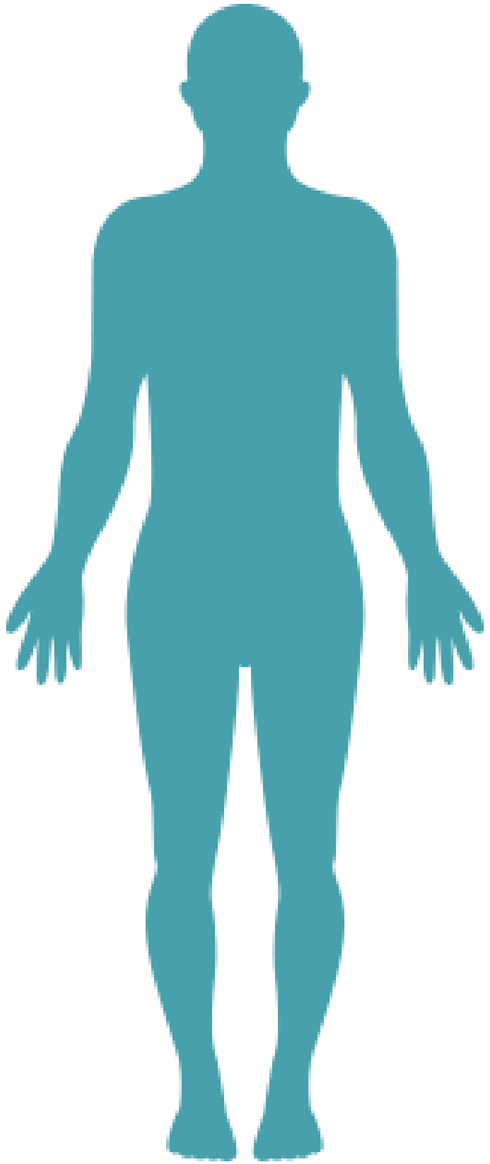
MAGNETIC NANOPARTICLES: APPLICATIONS



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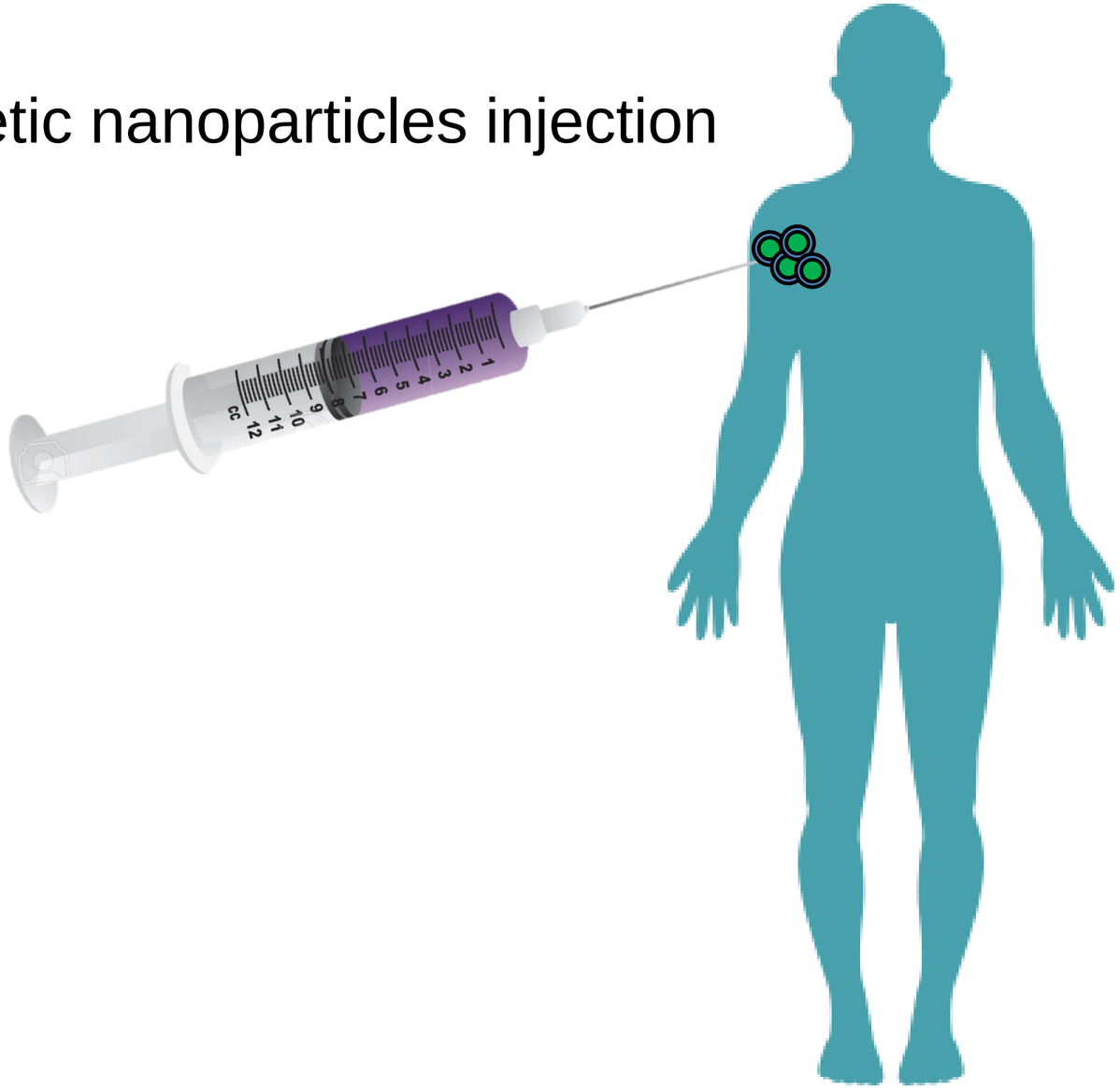
MAGNETIC NANOPARTICLES: APPLICATIONS

Magnetic nanoparticles injection



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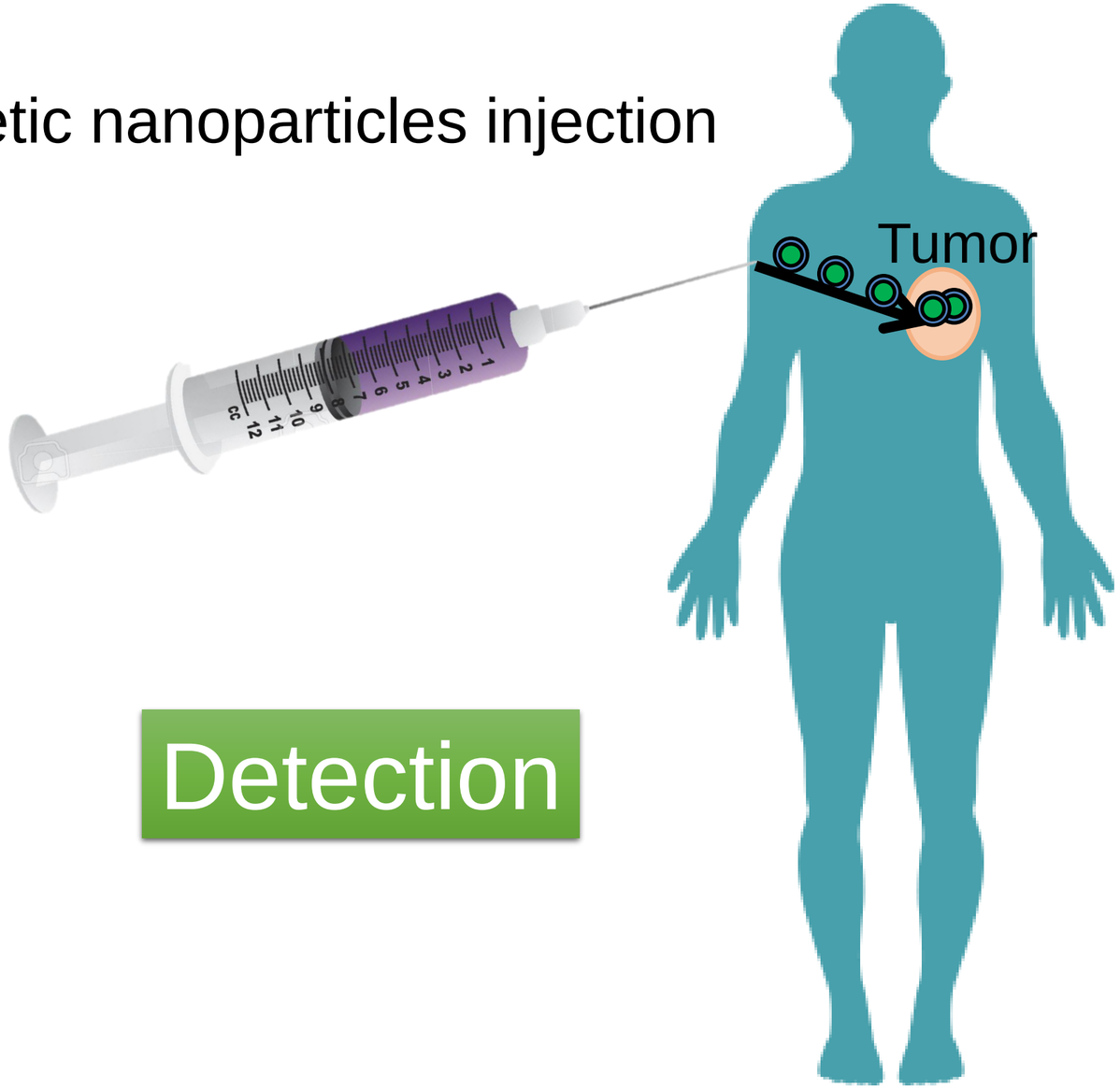
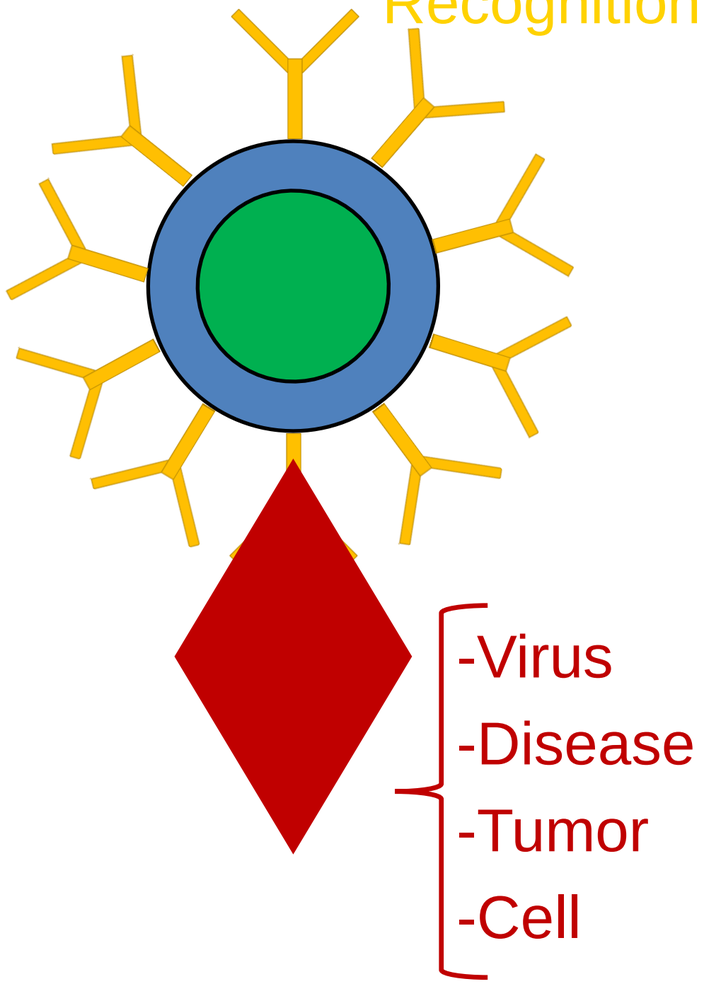
MAGNETIC NANOPARTICLES: APPLICATIONS

Magnetic nanoparticles injection



Detection



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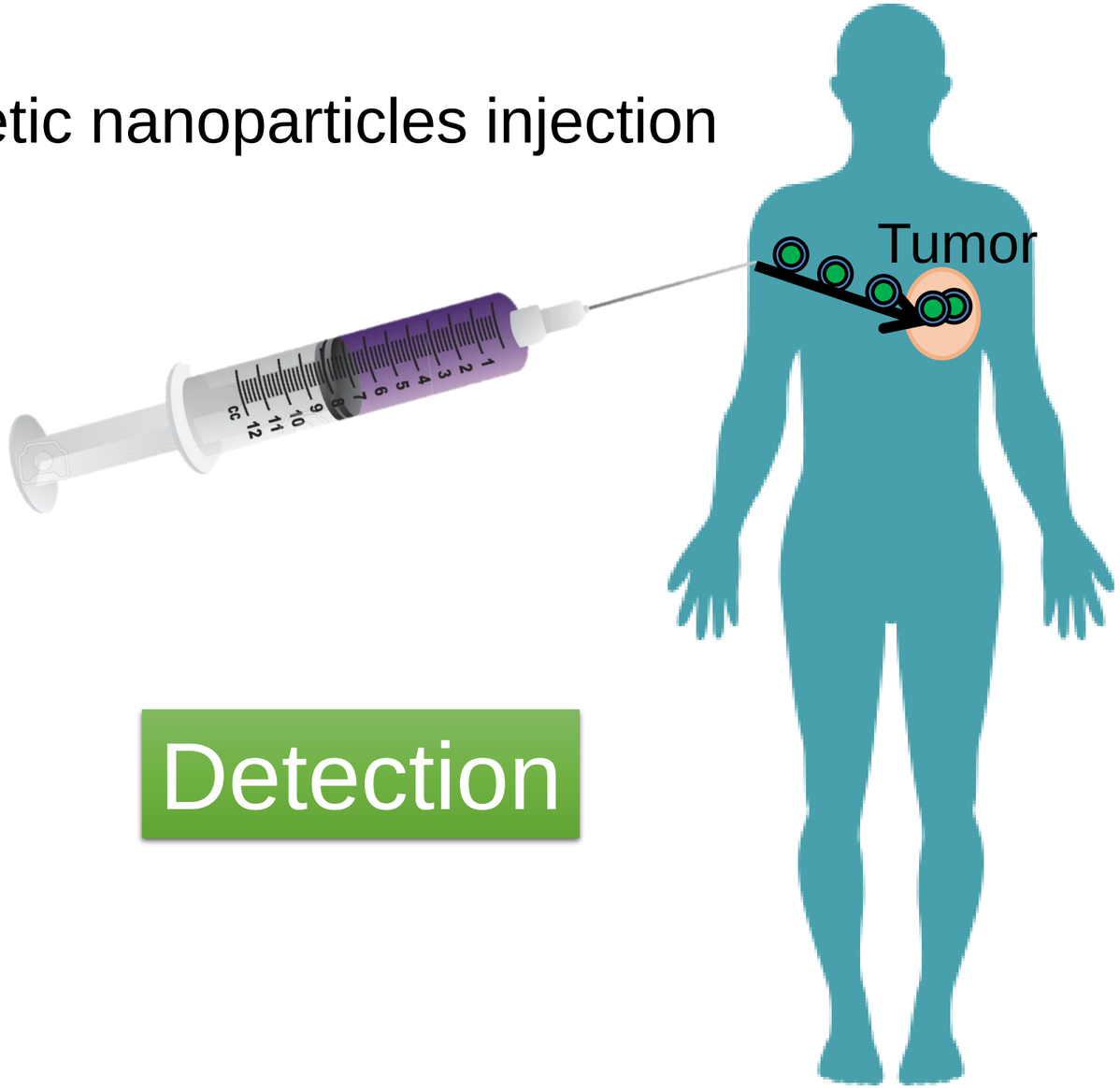
MAGNETIC NANOPARTICLES: APPLICATIONS

Magnetic nanoparticles injection



Adapted from https://www.youtube.com/watch?v=1QwyMWM0Jjg

Detection

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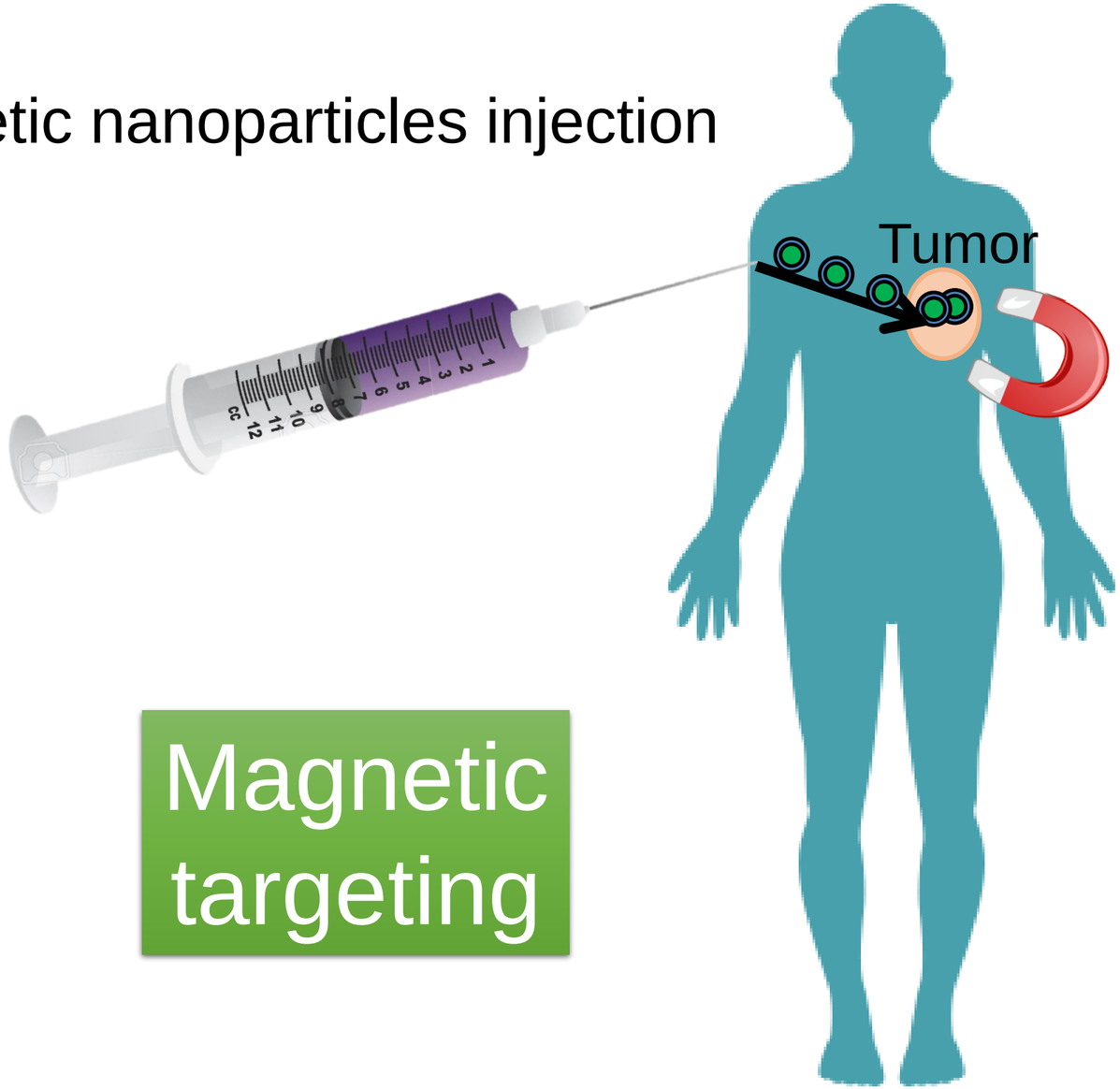
MAGNETIC NANOPARTICLES: APPLICATIONS

Magnetic nanoparticles injection



Magnetic targeting

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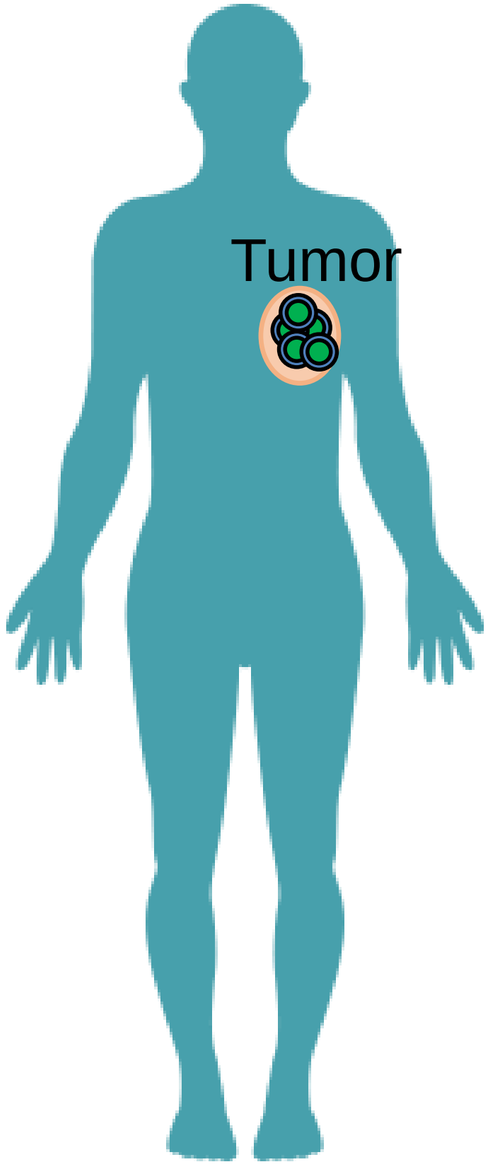
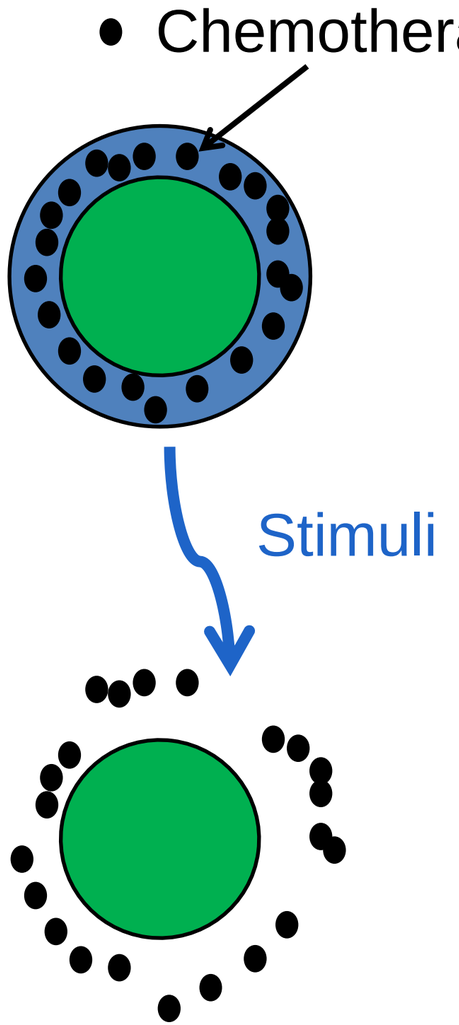
MAGNETIC NANOPARTICLES: APPLICATIONS



Drug release



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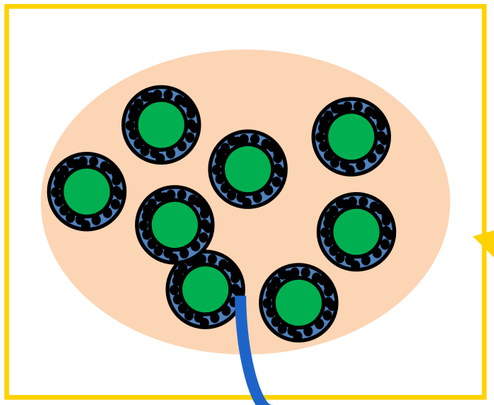
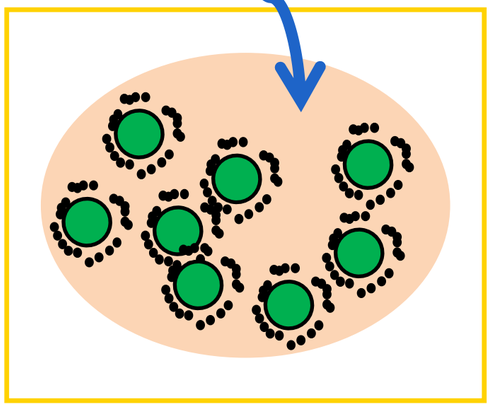
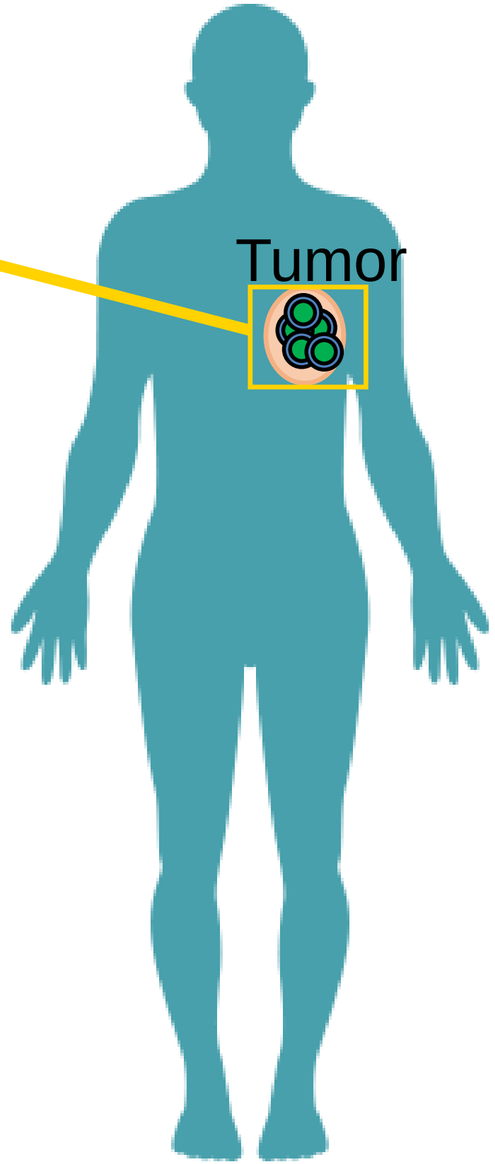
MAGNETIC NANOPARTICLES: APPLICATIONS

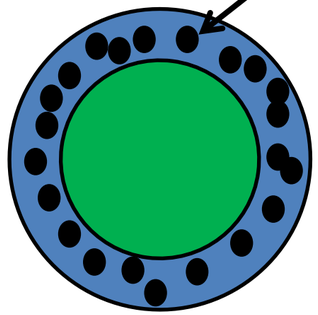




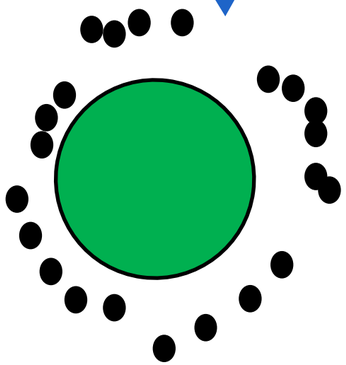
Drug release



- Chemotherapeutics



Stimuli



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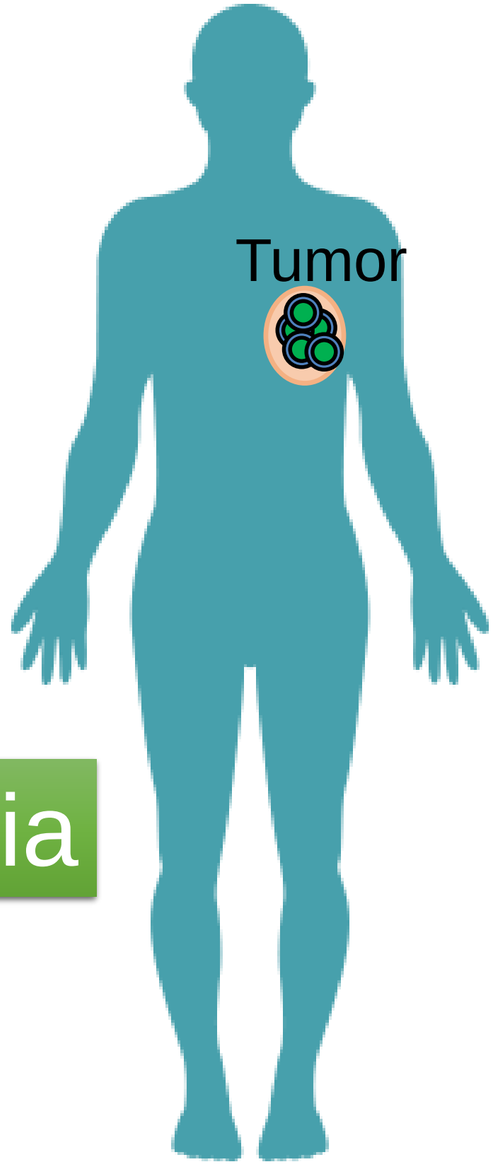
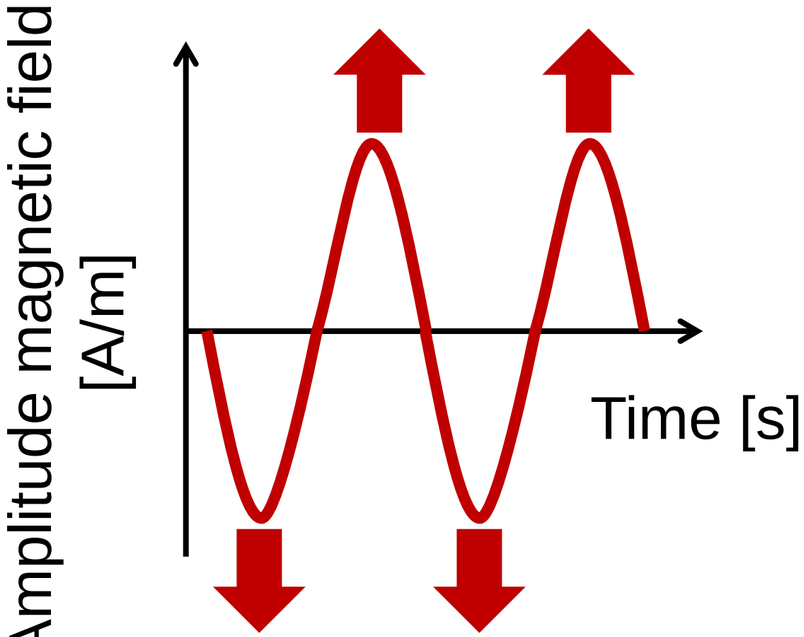
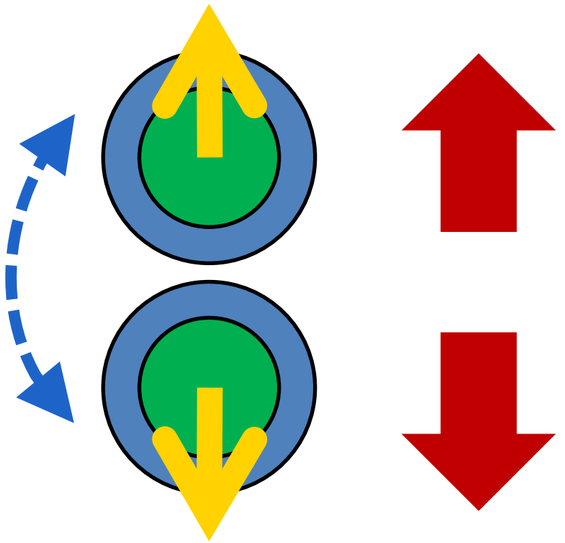
MAGNETIC NANOPARTICLES: APPLICATIONS



Hyperthermia





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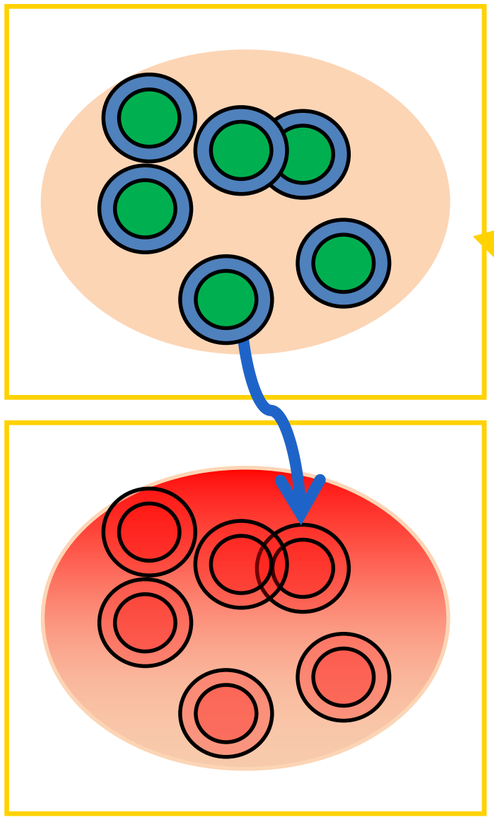
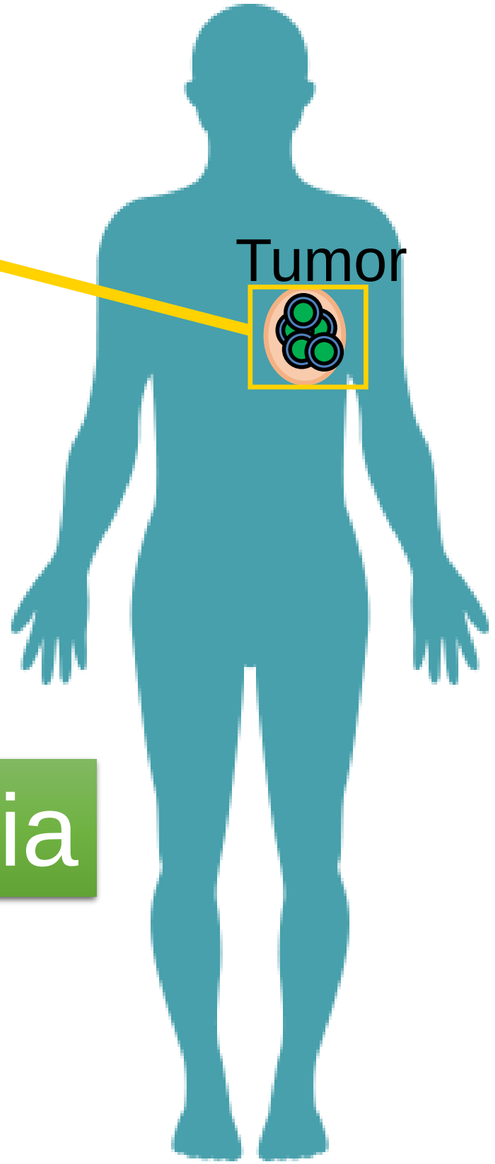
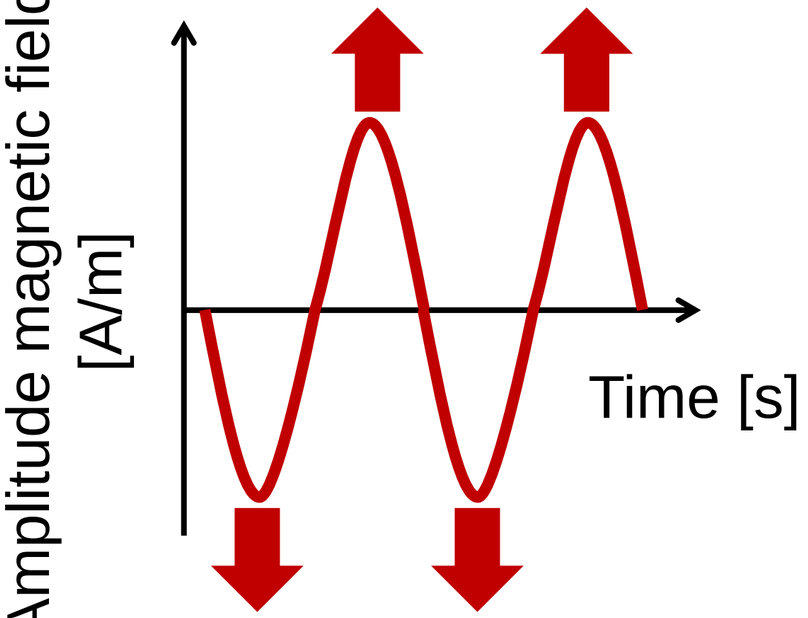
MAGNETIC NANOPARTICLES: APPLICATIONS

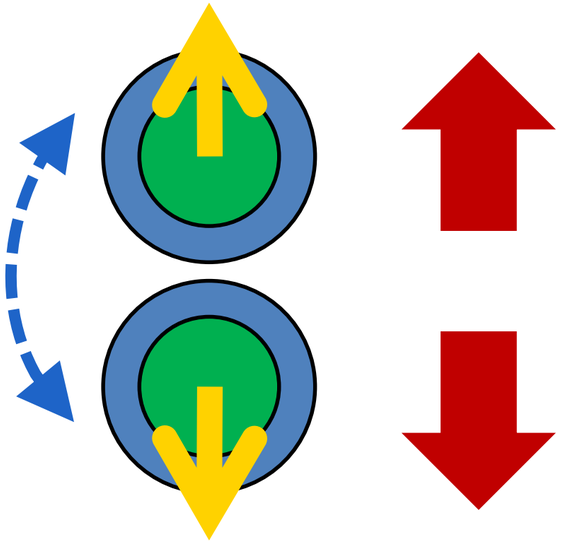


Temperature increase



Hyperthermia





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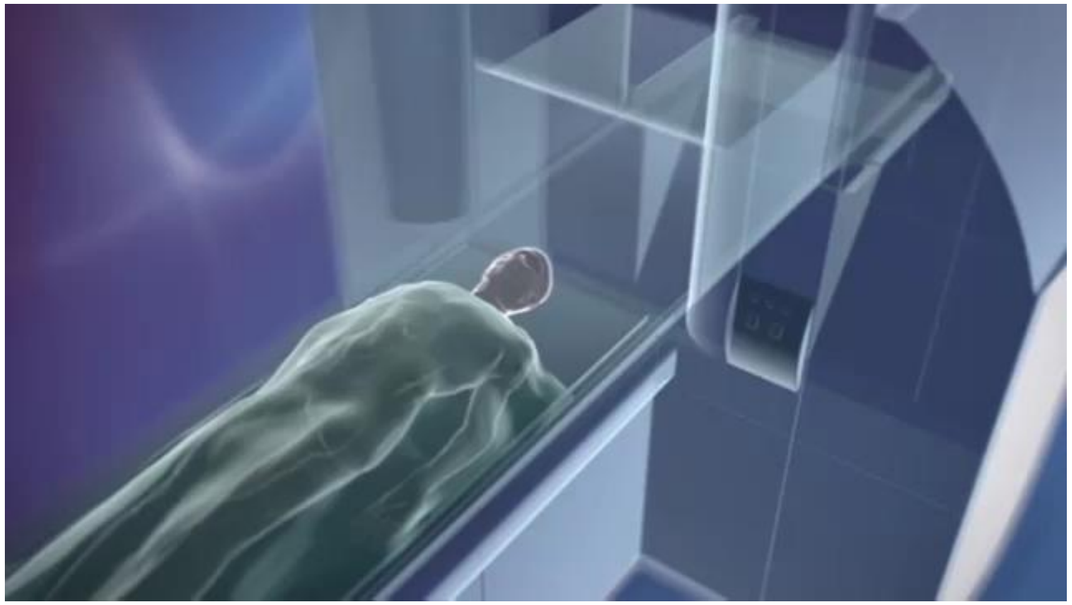
MAGNETIC NANOPARTICLES: APPLICATIONS



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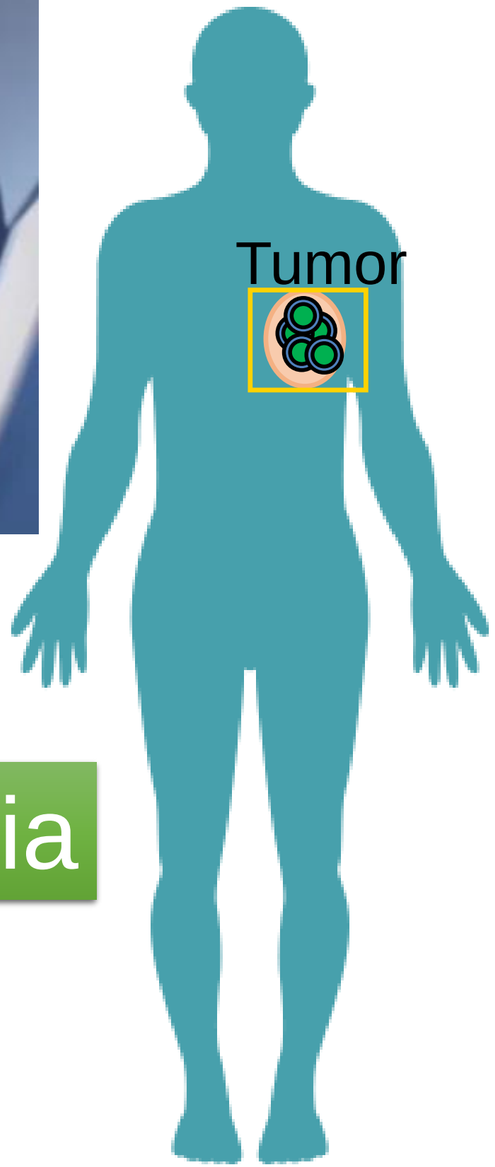
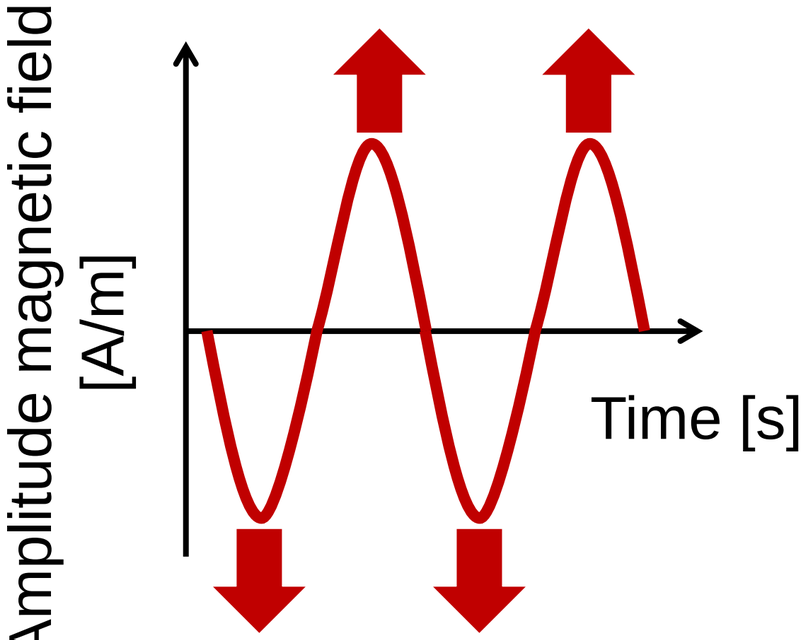
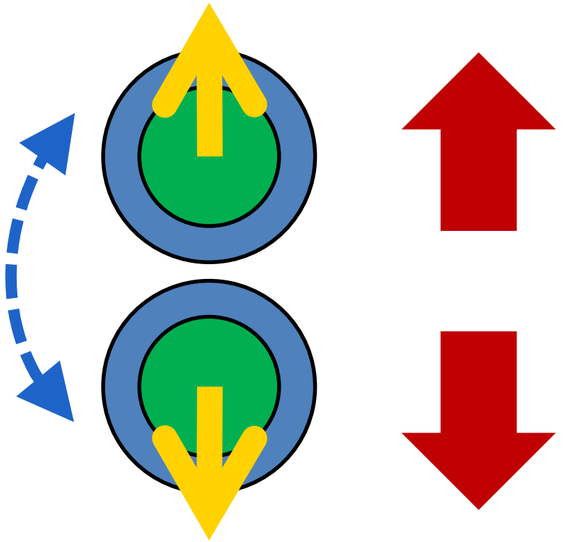




Hyperthermia



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MAGNETIC NANOPARTICLES: APPLICATIONS

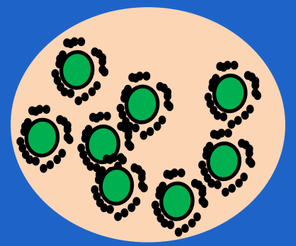
THERANOSTICS

THERAPY

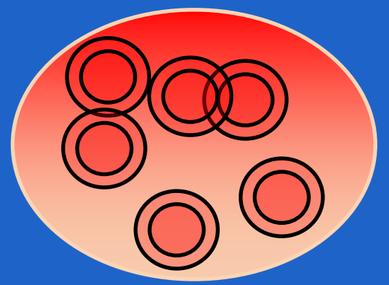
+

DIAGNOSTICS

Drug delivery



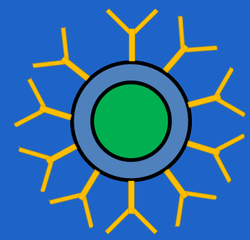
Hyperthermia



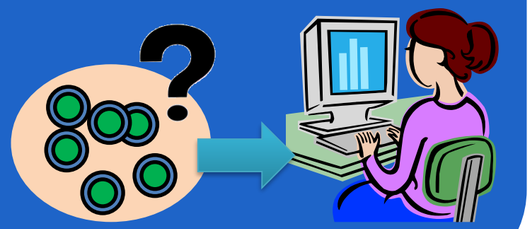
Particles successful at both

Provide personal treatment

Detection



Therapy progress



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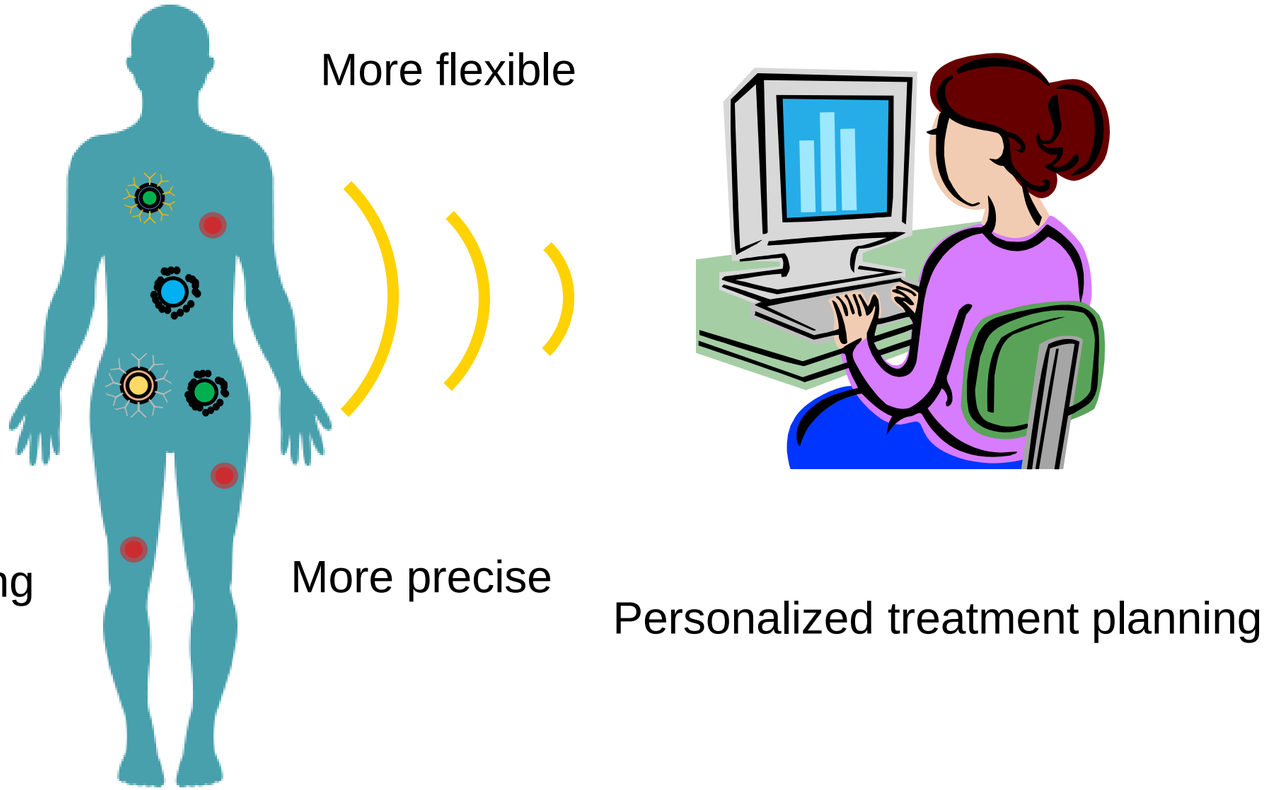
Combine applications in a single medical examination

THERANOSTICS: IMPROVED PATIENT OUTCOMES

Theranostic platform simultaneously provides *diagnostic* and *therapeutic* services

Necessary step towards personalized medicine



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BIOMEDICAL APPLICATIONS OF MAGNETIC NANOPARTICLES:

CONTRAST ENHANCEMENT

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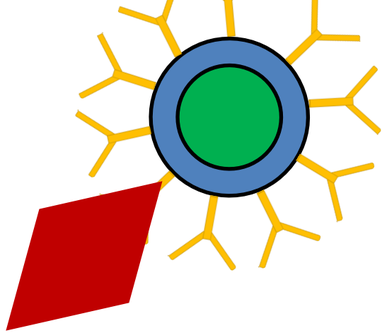
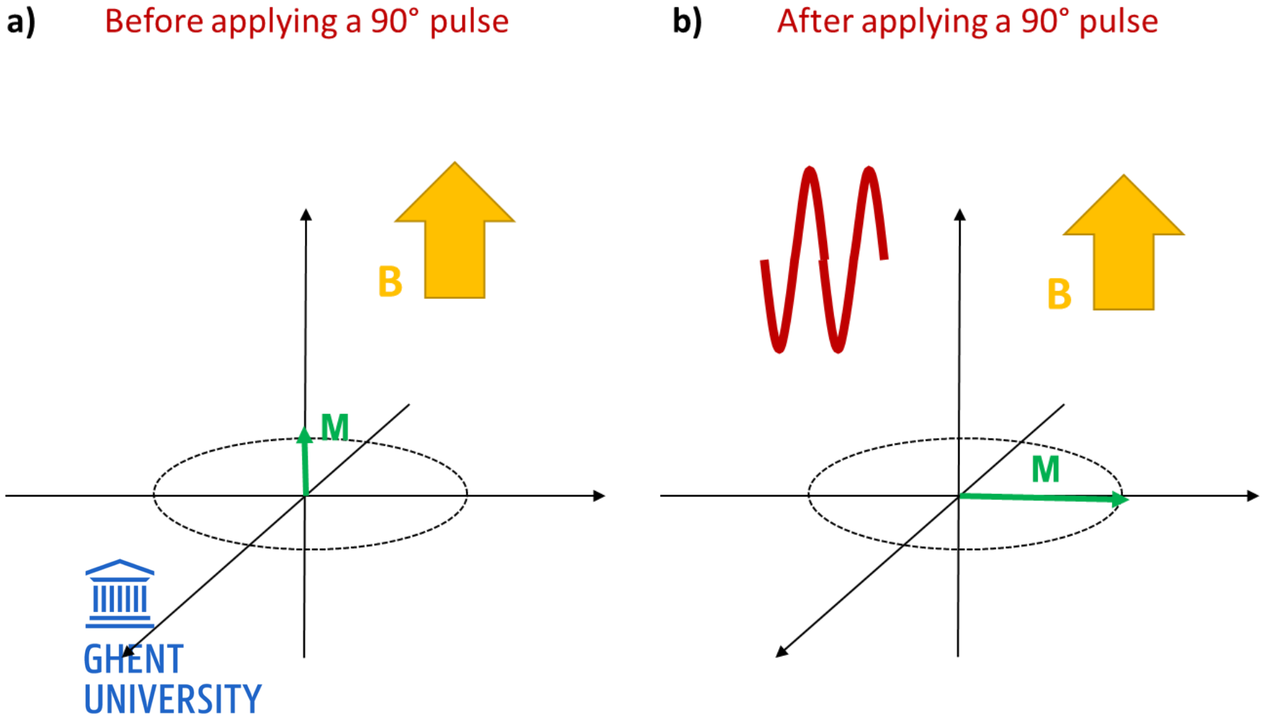
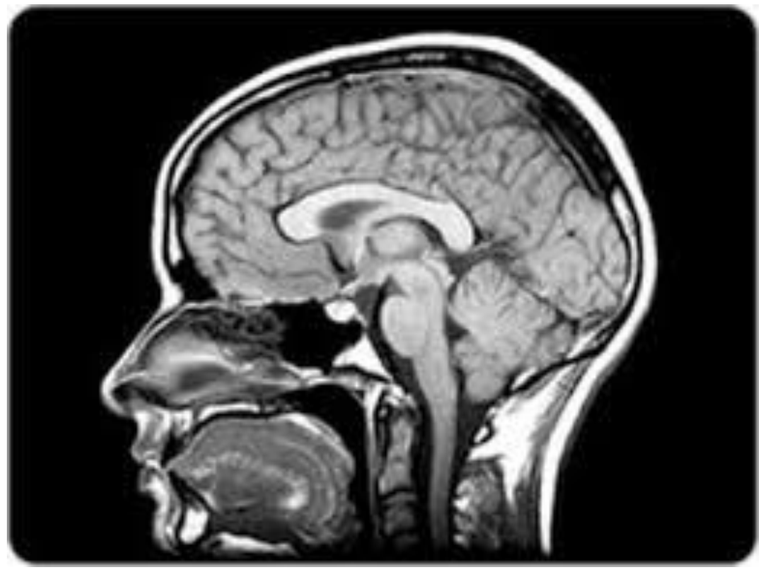
CONTRAST ENHANCEMENT: MRI



Magnetic nanoparticles to give more contrast where needed and to allow *molecular Imaging*, i.e. follow up of biological processes by visualizing cells and molecules

MNP bind to molecules and cells allowing their visualisation





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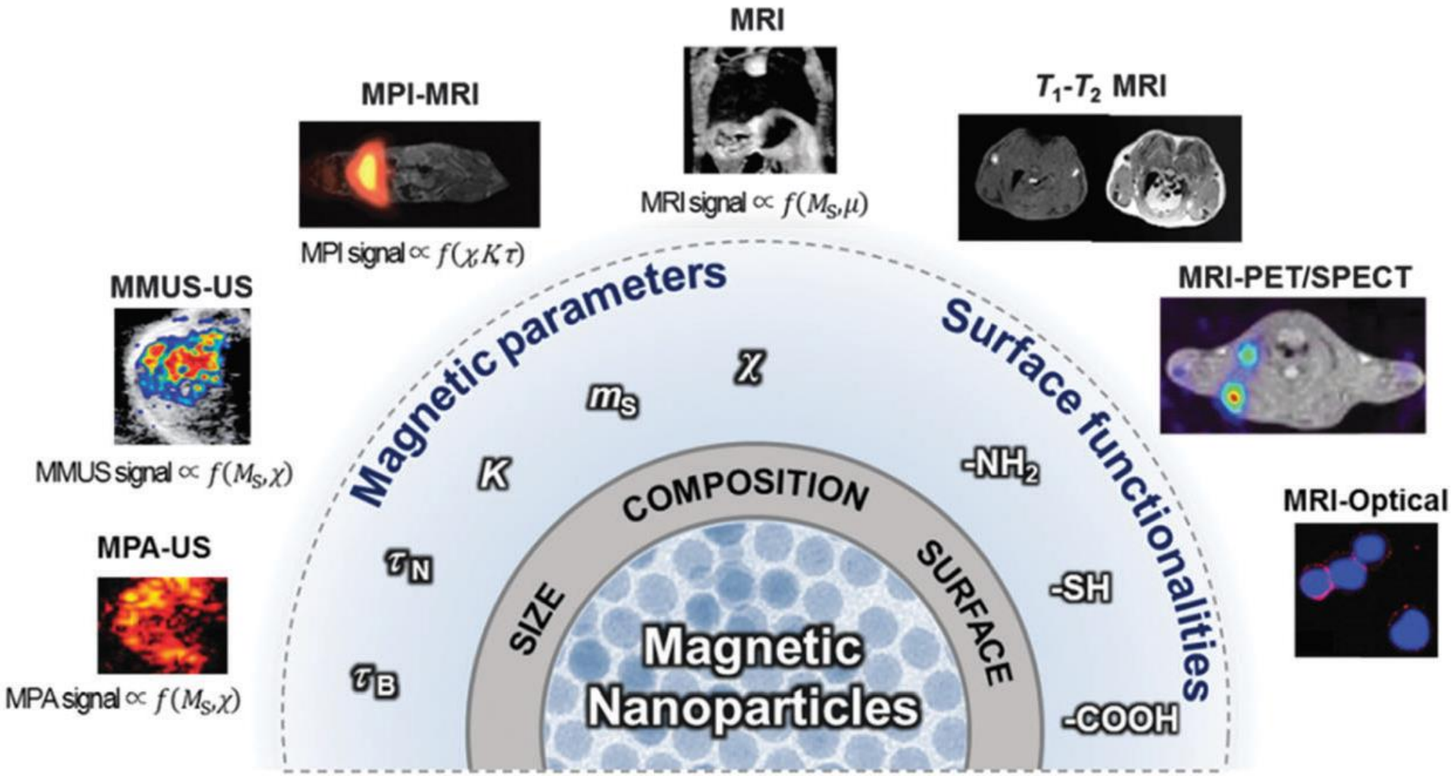
CONTRAST ENHANCEMENT: MRI

T_2 contrast agent: high magnetic moment, as this changes the local field of the protons and hence, the protons dephase faster: larger core sizes (**m** is proportional to V_c), changing the particle's composition (metal doping to boost M_{sat})

T_1 contrast: having unpaired electrons at the surface of the particle (canted surface spins) that improve energy exchange with the protons, by decreasing particle size and doping the particle with rare-earth metals that disrupt spin ordering



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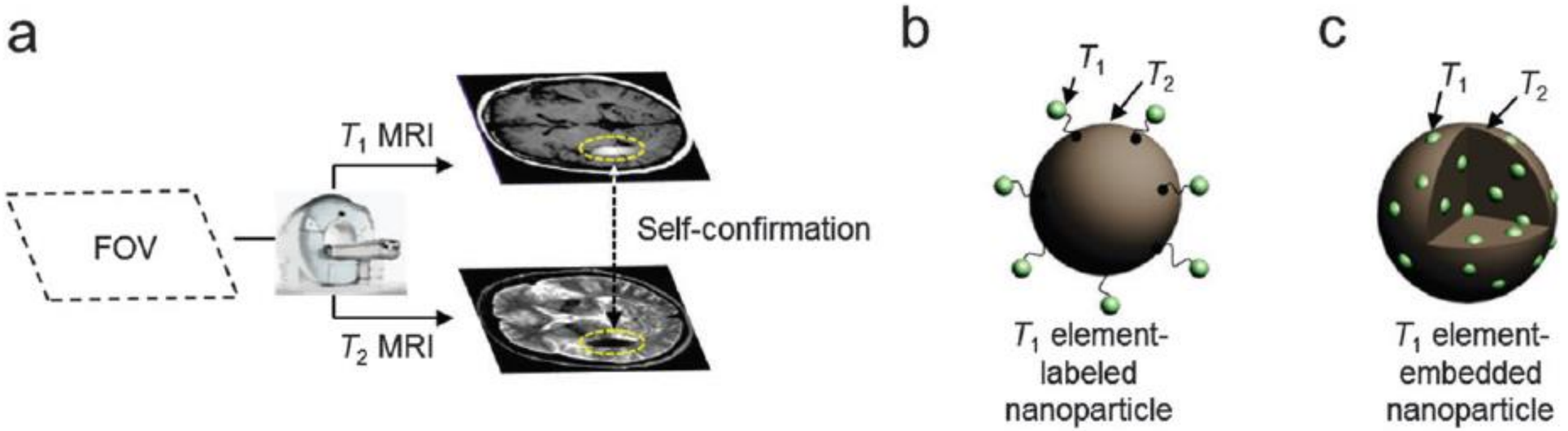
CONTRAST ENHANCEMENT: MRI

MNP with high T_2 contrast can generate artifacts, which present themselves as dark regions, referred to as *blooming effects*. These blooming effects can obscure the pathological tissue and healthy tissue and therefore it is difficult to locate them. Furthermore, artifacts, which can be both dark or bright signals, arise in MRI images due to air, fat and blood clots. Therefore, it is hard to make the distinction between MNP signals, artifacts and low tissue signals.



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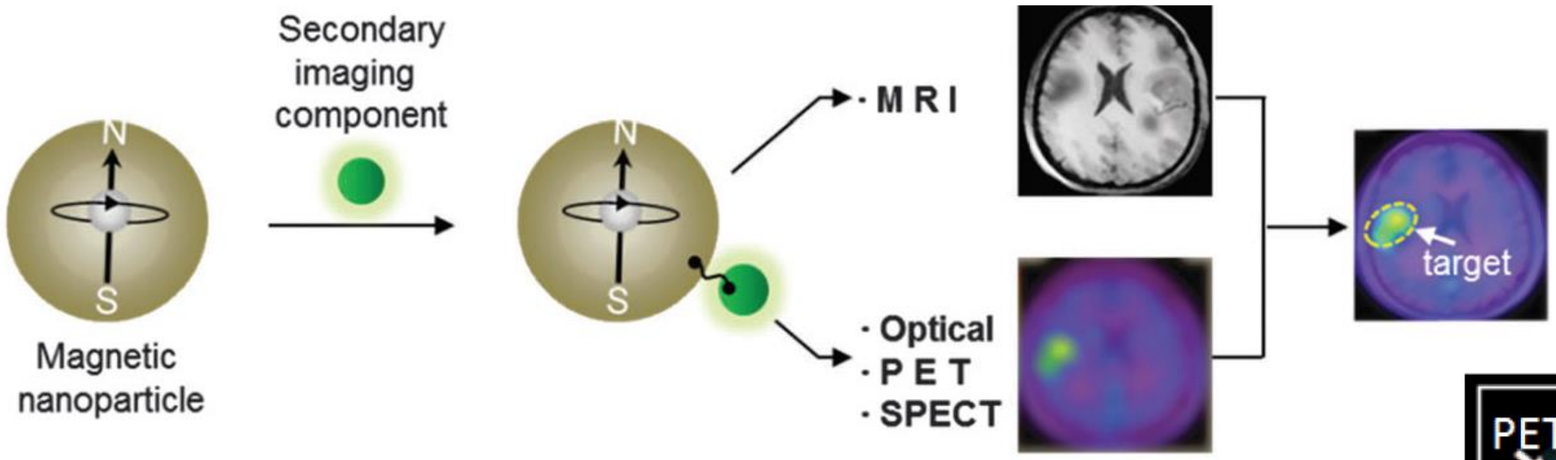
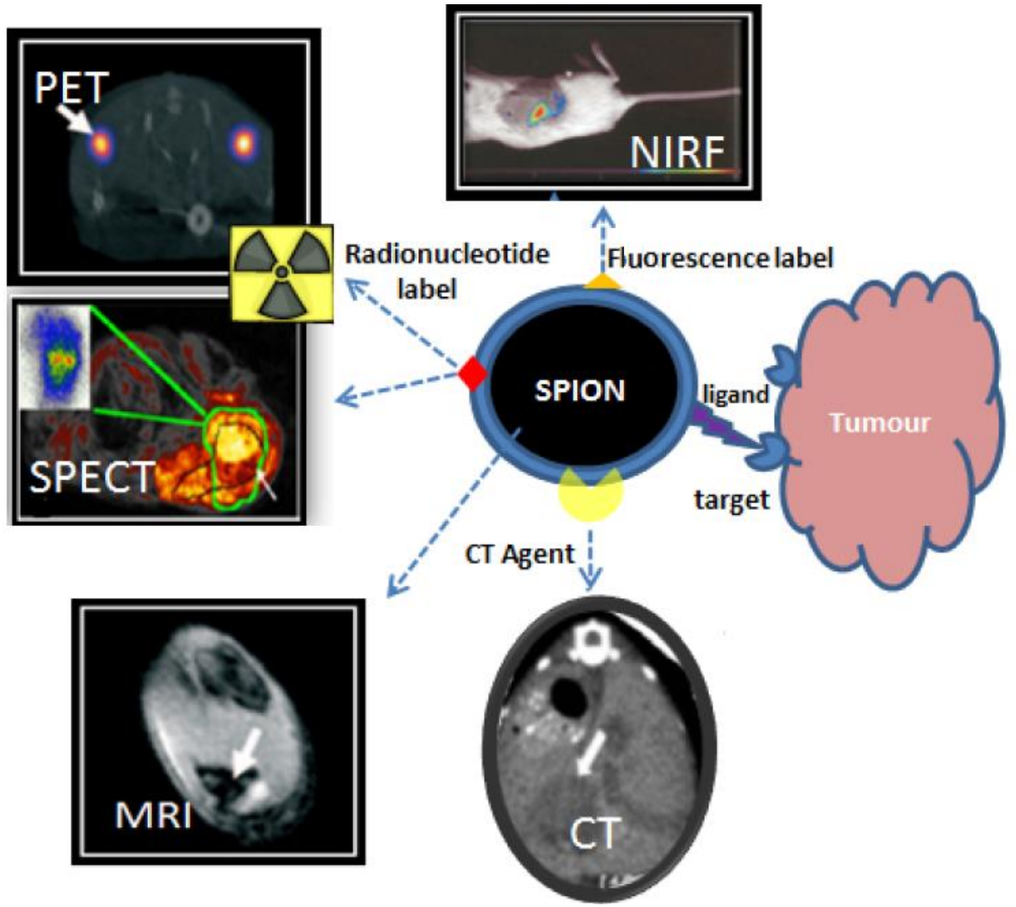
COTRAST ENHANCEMENT: MULTI-MODAL





Confirmation in multiple imaging modalities

Anatomic information

Stability and production difficult

Complex hardware combination

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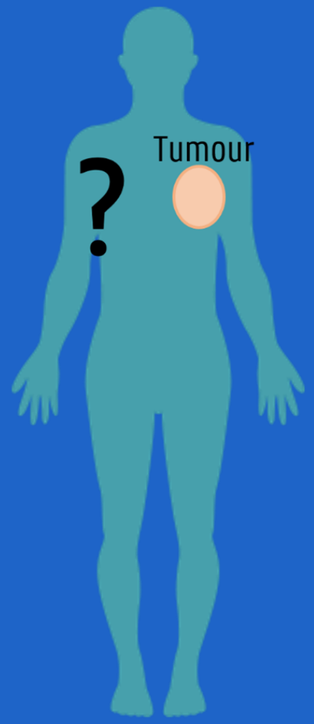
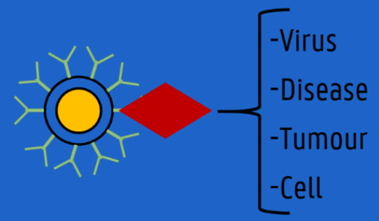
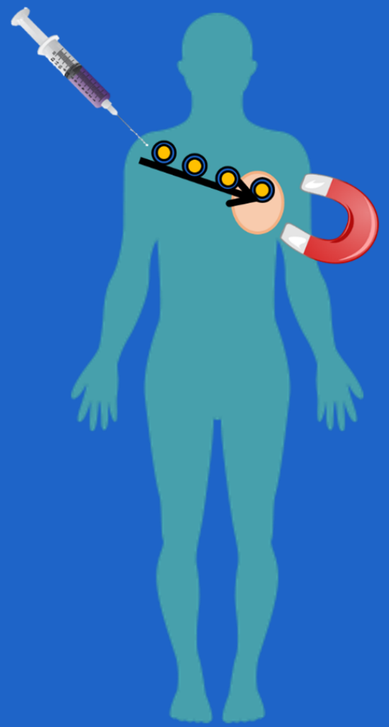
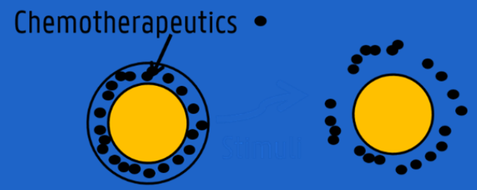
Disease detection



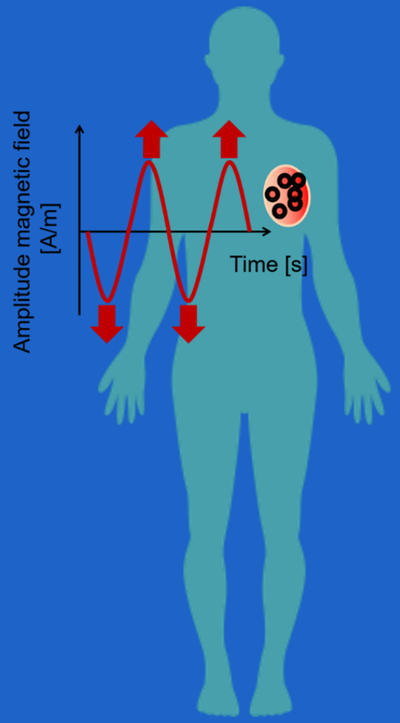


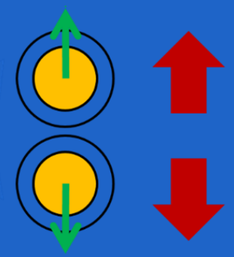
Magnetic targeting





Magnetic hyperthermia





MAGNETIC HYPERTHERMIA

MAGNETIC HYPERTHERMIA: INTRODUCTION

Traditional therapies:

- Radio-, chemotherapy: works on complete or large part of the body, side-effects
- Surgery: can contain risks, sometimes hard to reach

Magnetic hyperthermia:

- Means of precision heating *local* heating (e.g. tumor site)
- Less side effects
- Can be combined with other treatment modalities

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MAGNETIC HYPERTHERMIA: INTRODUCTION

Local temperature rise of tissue to inflect thermal damage

Exploits increased heat sensitivity of tumor cells

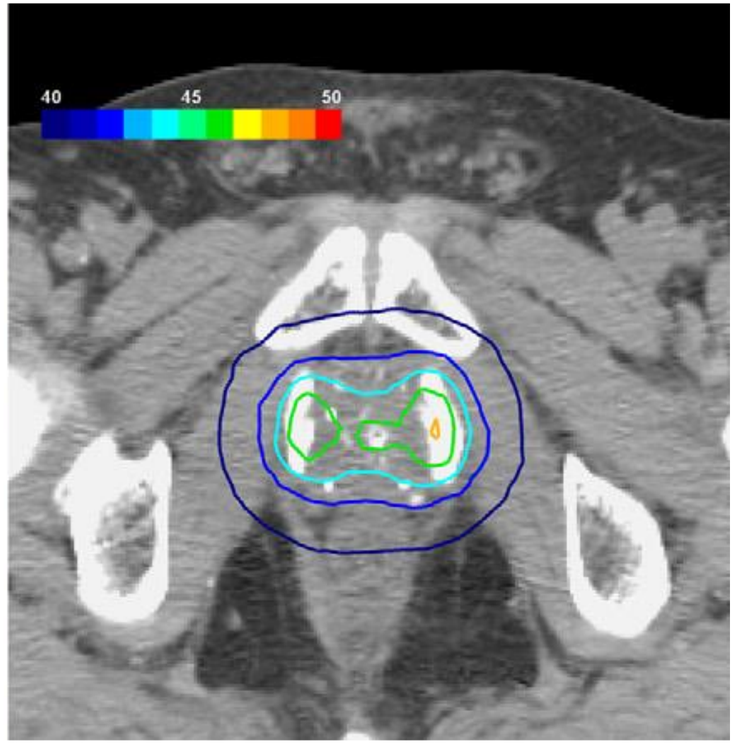
Thermoablation

Temperature range > 46 °C

Hyperthermia

Temperature range 41 – 46 °C

Duration varies from few minutes to hours



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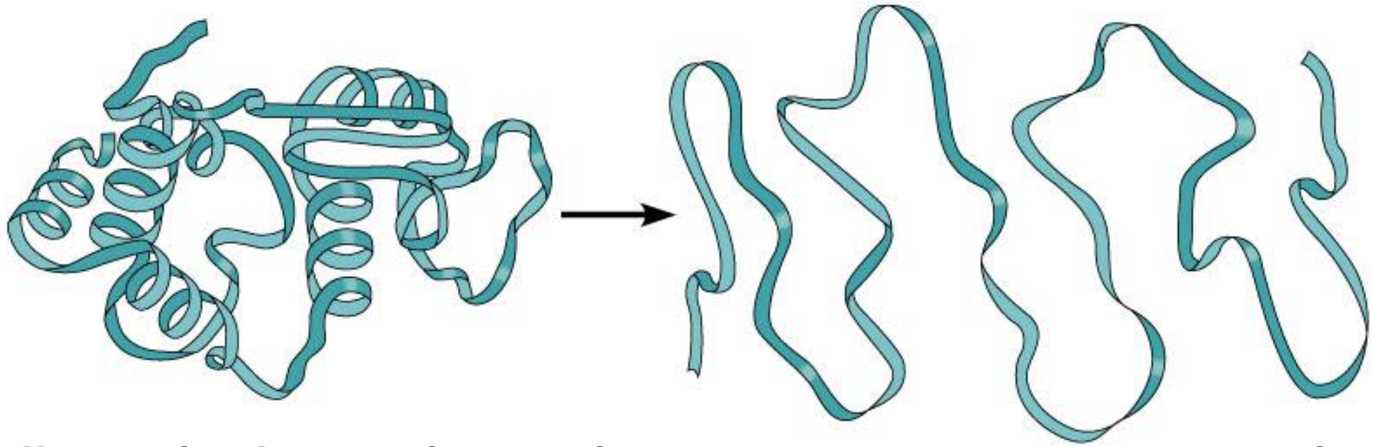
MAGNETIC HYPERTHERMIA: IMPACT ELEVATED TEMPERATURES

- Enzymatic and structural proteins denature



- Cell survival rate depends on type, temperature and exposure time
- Increased metabolic rate
- Physiological changes
- Heat shock response
- Immune response

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MAGNETIC HYPERTHERMIA: CONCEPT

- Magnetic nanoparticles (MNPs): generate heat when subjected to an alternating magnetic field (AMF) (Amplitude: < 50 kA/m, Frequency: 50 – 1200 KHz)

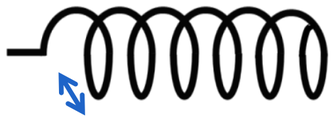
- Magnetic nanoparticle hyperthermia (MNH):

  1) suspension of MNPs in biocompatible fluids
  2) direct injection into site (chemical/magnetic targeting)
  3) subject to an AMF

✓ No attenuation of low-frequency AMF

✘ Radiofrequency AMFs induce eddy currents in the surrounding tissue

→ AMF's Magnitude x Frequency < 4.85 10^8 A/(ms)



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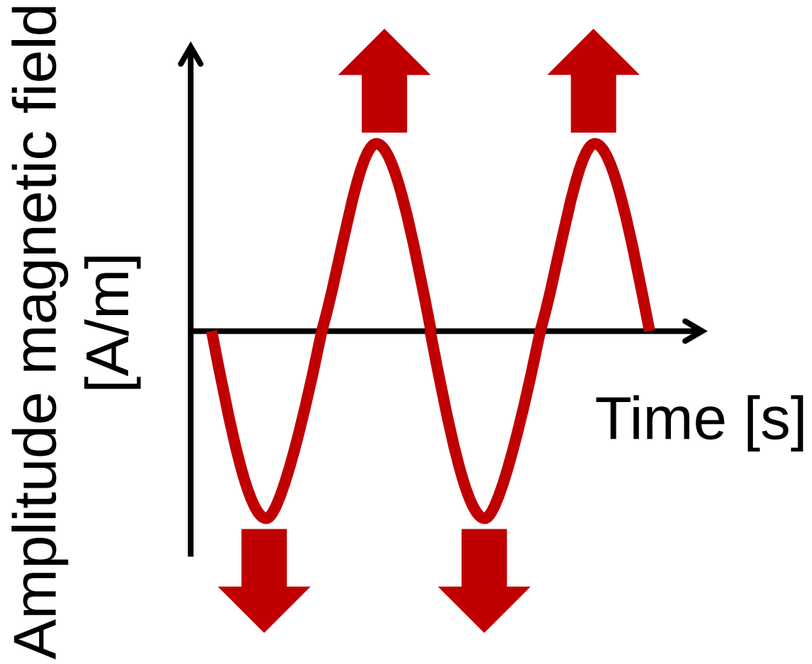
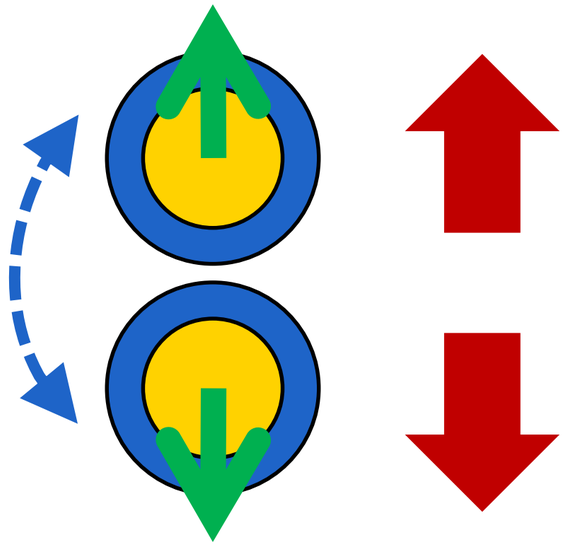
MAGNETIC HYPERTHERMIA: HEATING MODEL

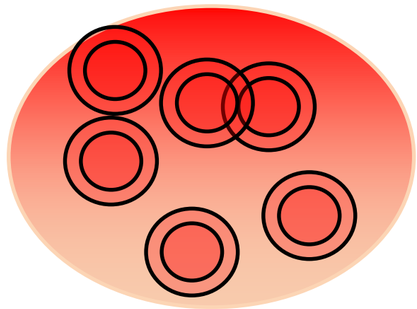
How do MNP generate heat?

~~Eddy currents?~~ Hysteretic losses ✓

Particles want to align themselves to the direction of the AMF







When frequency is too high, MNP cannot follow anymore and generate heat

(material, shape, size, etc.)

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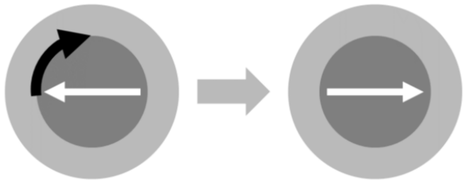
MAGNETIC HYPERTHERMIA: HEATING MODEL

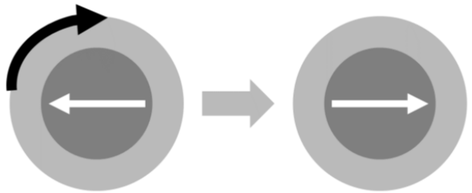
How do MNP align?

Néel relaxation



rotation of the particle's magnetic moment

Brownian relaxation

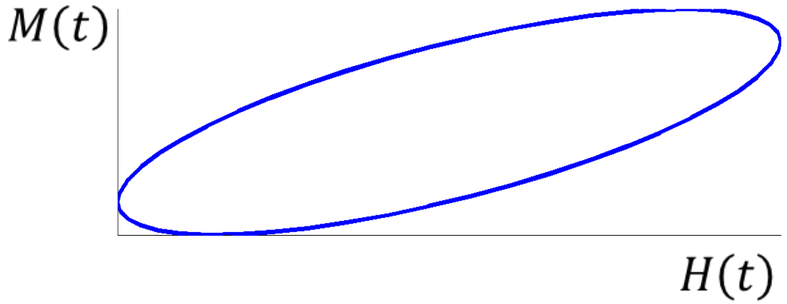


rotation of the particle as a whole

How much heat do MNP produce?

$$q_{source} \propto \int M(H)\mathrm{d}H$$

M: magnetization
H: applied magnetic field



- Linear response theory: dynamic response of an ensemble of non-interacting MNP

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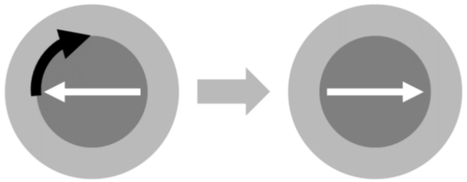
MAGNETIC HYPERTHERMIA: HEATING MODEL

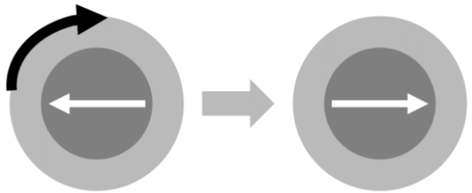
How do MNP align?

Néel relaxation



rotation of the particle's magnetic moment

Brownian relaxation

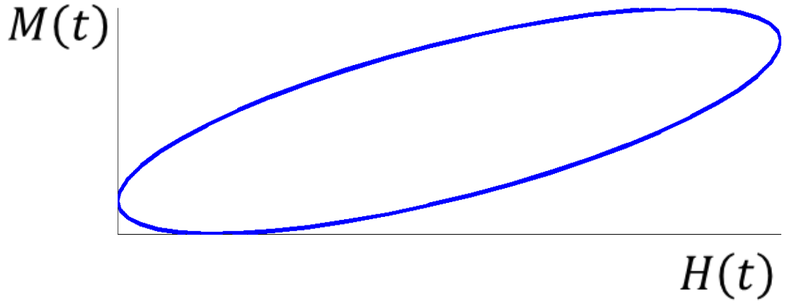


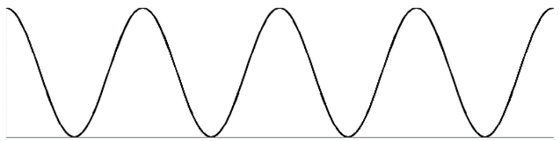
rotation of the particle as a whole

How much heat do MNP produce?

$$q_{source} \propto \int M(H)\mathrm{d}H$$

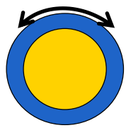
M: magnetization
H: applied magnetic field

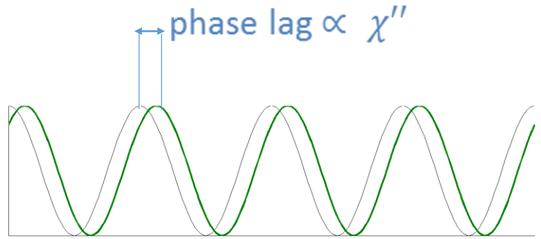




$$H(t) = H_a \cos(\omega t) \qquad \omega = 2\pi f$$

Amplitude & frequency





$$M(t) = H_a(\chi' \cos(\omega t) + \chi'' \sin(\omega t))$$

Susceptibility $\chi = \chi' + i\chi''$

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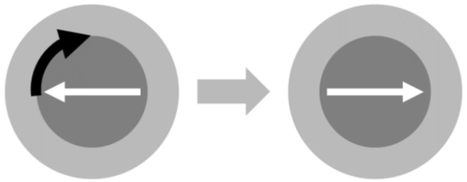
MAGNETIC HYPERTHERMIA: HEATING MODEL

How do MNP align?

Néel relaxation



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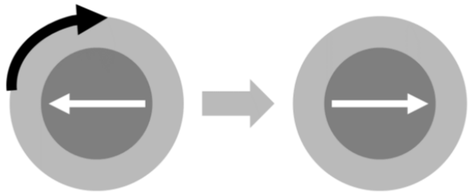

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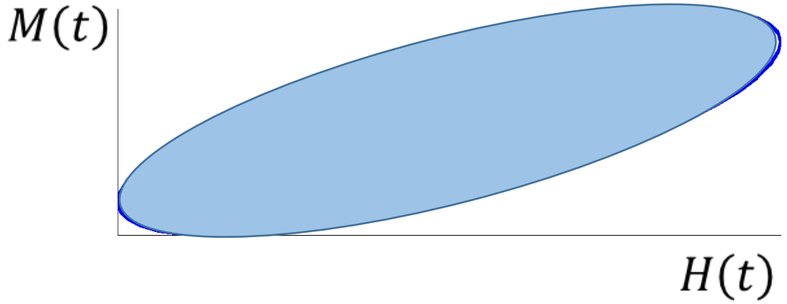

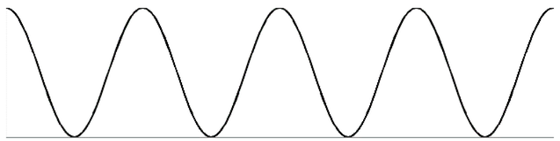

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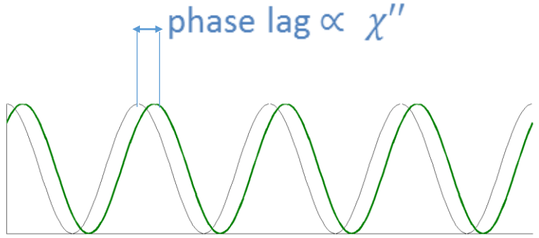
Amplitude & frequency



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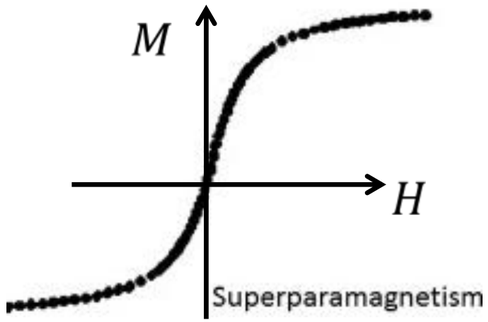
MAGNETIC HYPERTHERMIA: HEATING MODEL

Magnetic nanoparticle heating model: linear response theory (LRT)

- Assumptions: linear relationship between M and H, no interaction between particles



$$\mathbf{M} = \chi_0 \mathbf{H}$$ (In quasi-static regime)

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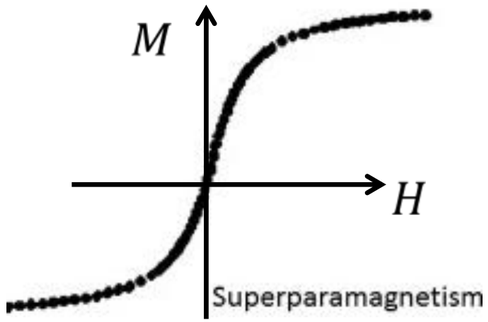

$$\mathbf{M} = \chi_0 \mathbf{H}$$ (In quasi-static regime)

- Loss component of the magnetic susceptibility:

$$\chi' = \chi_0 \frac{1}{1 + (2\pi f \tau_{\text{eff}})^2}$$

$$\chi'' = \chi_0 \frac{2\pi f \tau_{\text{eff}}}{1 + (2\pi f \tau_{\text{eff}})^2}$$

Zero-field simplification

$$\tau_{\text{eff}}(V_c, V_h) = \frac{\tau_N(V_c)\tau_B(V_h)}{\tau_N(V_c) + \tau_B(V_h)}$$

V_c = Magnetic core volume
V_h = Complete particle volume

$$\tau_N = \tau_0 \exp\left(\frac{\Delta E}{k_B T}\right)$$

$$\tau_B = \frac{3\eta V_h}{k_B T}$$

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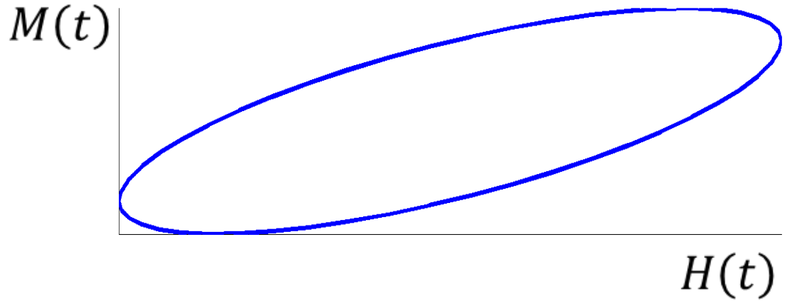
$$\longrightarrow \quad \mathbf{M} = \chi \mathbf{H}$$



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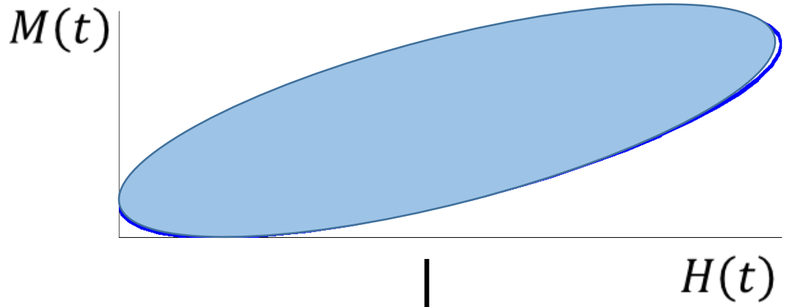

$$q_{source} \propto \int M(H)\mathrm{d}H$$

- Specific Loss Power (SLP) [W/g] of MNP:

$$\text{SLP} = \frac{\mu_0 f}{\rho_c} \int M(H)\mathrm{d}H$$

Mass density of magnetic material

$$\text{SLP} = \frac{\mu_0}{\rho_c} \chi_0 \pi f H^2 \frac{2\pi f \tau_{\text{eff}}}{1 + (2\pi f \tau_{\text{eff}})^2}$$

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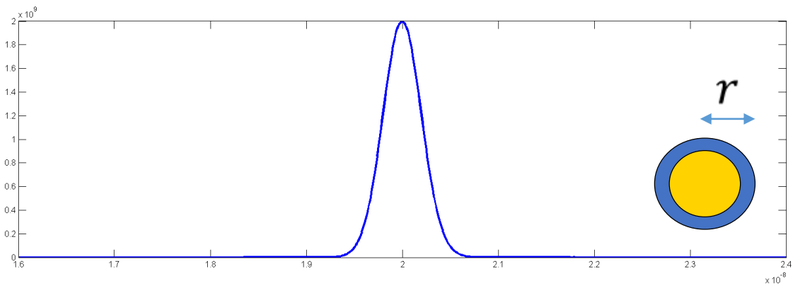
MAGNETIC HYPERTHERMIA: HEATING MODEL

$$< SLP_{\mathrm{LRT}} >= \int_0^{\infty} SLP(r) \cdot p(r)\, \mathrm{d}r$$

$$\mathrm{SLP} = \frac{\mu_0}{\rho_c} \chi_0 \pi f H^2 \frac{2\pi f \tau_{\mathrm{eff}}}{1 + (2\pi f \tau_{\mathrm{eff}})^2}$$

Lognormal propability density function of MNP radii:

$p(r)$



$$p(r) = \frac{1}{\sigma_r r \sqrt{2\pi}} \exp\left[\frac{-\ln^2(r/\mu_r)}{2\sigma_r^2}\right]$$

$$\chi' = \chi_0 \frac{1}{1 + (2\pi f \tau_{\mathrm{eff}})^2}$$

$$\chi'' = \chi_0 \frac{2\pi f \tau_{\mathrm{eff}}}{1 + (2\pi f \tau_{\mathrm{eff}})^2}$$

$$\tau_{\mathrm{eff}}(V_c, V_h) = \frac{\tau_N(V_c)\tau_B(V_h)}{\tau_N(V_c) + \tau_B(V_h)}$$

V_c = Magnetic core volume
V_h = Complete particle volume

$$\tau_N = \tau_0 \exp\left(\frac{\Delta E}{k_B T}\right)$$

$$\tau_B = \frac{3\eta V_h}{k_B T}$$

$$\Delta E = K V_c$$

K = anisotropy constant, η = viscosity

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MAGNETIC HYPERTHERMIA: HEATING MODEL

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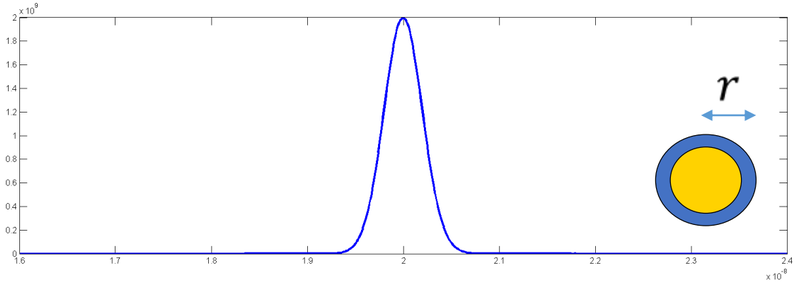

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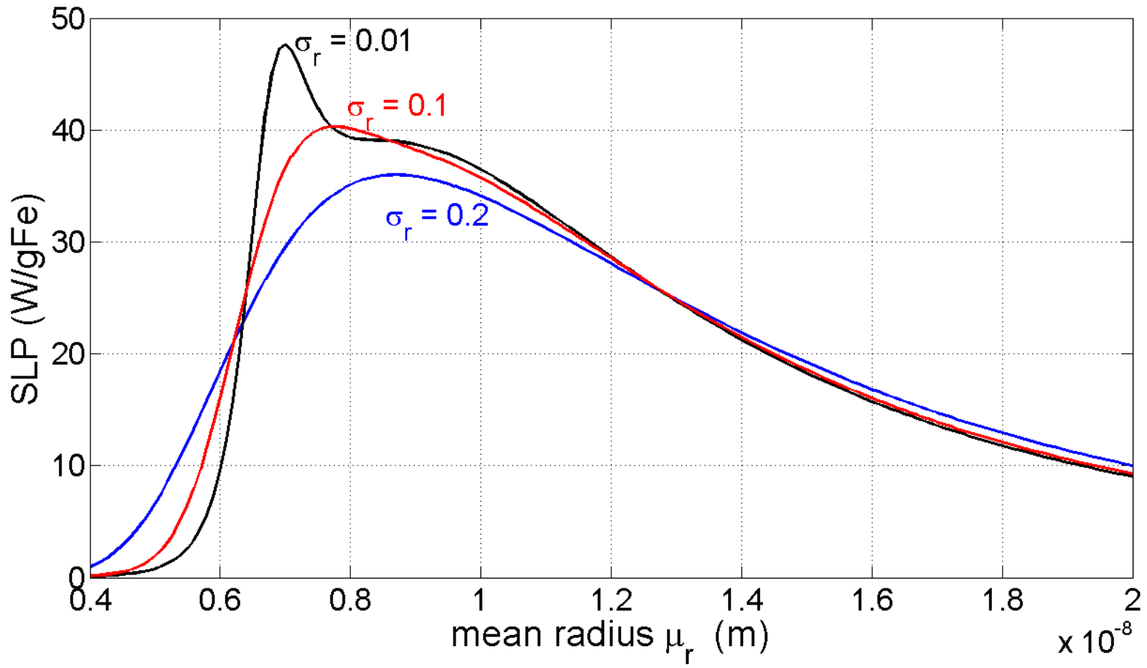

Attention!

Larger particles not single-domain!

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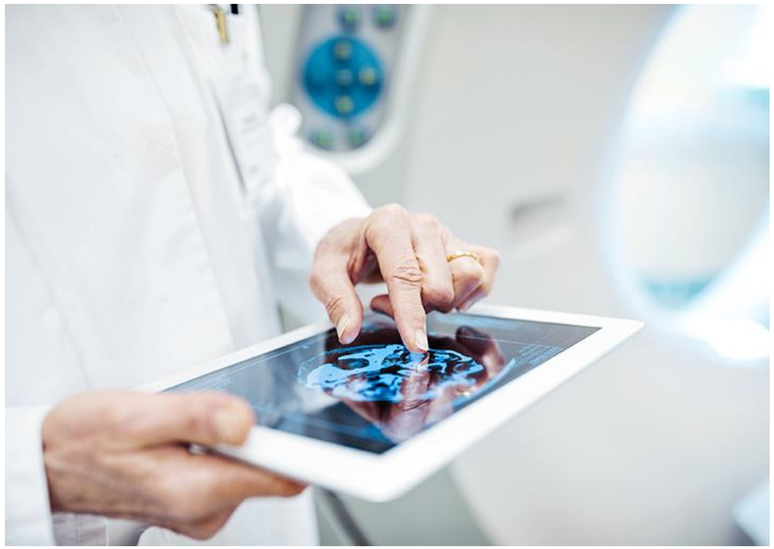
MAGNETIC HYPERTHERMIA: CANCER

US: study with 120 patients

Goal: destruction of tumor cells

magforce®
THE NANOMEDICINE COMPANY

Europe (Germany):
Treatment of brain tumors (90 patients)
Pilot studies treatment pancreatic, prostate, breast cancer (80 patients)



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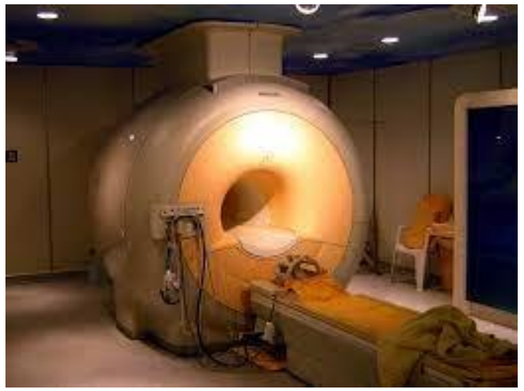
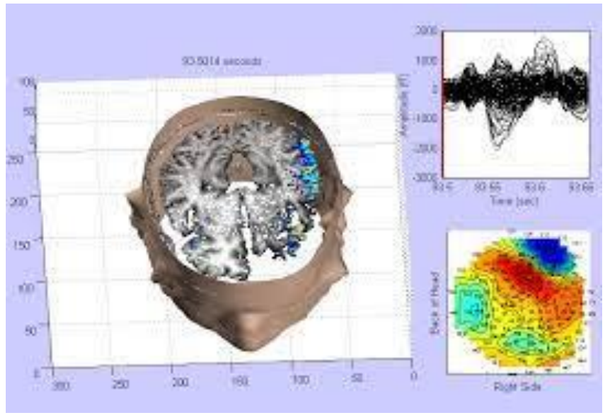
CONCLUSIONS

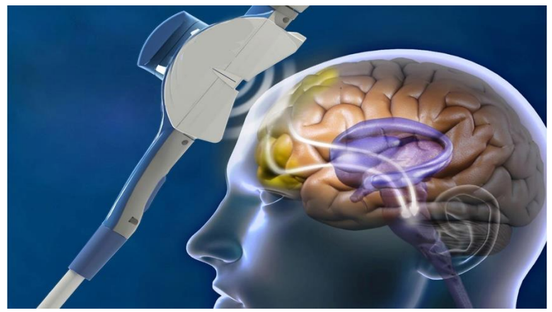
Many applications of magnetism in biology and medicine



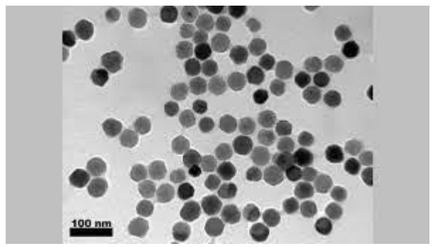
MRI



Neuromagnetism



Magnetic stimulation



Magnetic nanoparticles

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